BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s): G.J. Gormley et al.

Application Number: 10/010,678 Case No.: 19109DE

Filing Date: December 7, 2001

Title of the Invention: TRANSDERMAL TREATMENT WITH 5-ALPHA-REDUCTASE INHIBITORS *(as amended)*

Examiner: V. Y. Kim

Art Unit: 1618

REPLY BRIEF

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MERCK & CO., INC.

By _____ Date May 23, 2006

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This is in response to the Examiner's answer filed March 23, 2006, which in turn, is in response to the appeal brief filed December 16 2005, appealing from the Office Action mailed May 6, 2005.

REAL PARTY IN INTEREST

There is no change to the real party in interest.

RELATED APPEALS AND INTERFERENCES

There is a judicial proceeding related to the present application, the patent infringement litigation commenced by Merck against Dr. Reddy's Laboratories, Ltd., and Dr. Reddy's Laboratories, Inc., in the United States District Court for the District of Delaware, Civil Action No. 04-1313, involving United States Patent Nos. 5,547,957 and 5,571,817. The present application claims priority from a chain of applications including US 5,547,957 (USSN 214,915, filed March 17, 1994), and its parent USSN 138,500, filed October 15, 1993. A Stipulation of Dismissal was filed with the District Court on May 18, 2006, and a copy is enclosed in the APPENDIX.

As stated previously, there are no related appeals or interferences known to the Appellants, or known to Appellants' legal representative, that will directly affect the Board's decision in the pending appeal, other than the earlier appeal in the present application, Appeal No. 2004-0543, decision mailed December 29, 2004, previously provided with the Appeal Brief.

STATUS OF CLAIMS

There are no changes to the Claim status.

STATUS OF AMENDMENTS

There are no changes to the status of amendments.

SUMMARY OF CLAIMED SUBJECT MATTER

There are no changes in the Summary of Claimed Subject Matter. A copy of the claims appears in the CLAIMS APPENDIX.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There remains one issue being presented for review by the Board of Appeals. The issue on appeal is the rejection of Claims 28-37 under 35 U.S.C. § 103(a) as being unpatentable over Goldman, US 5,407,944. Appellants believe the rejection to be erroneous. Reading the Appeal Brief together with the Examiner's Answer thereto, it is clear that the remaining issue in the case is the interpretation of the phrases "consisting essentially of" and "consisting essentially of. . . as the active ingredient" as employed in the Claims 28-37.

ARGUMENT

I. "Consisting essentially of" precludes the presence of additional active agents for hair growth in Claims 28 to 37

The methods for treating androgenic alopecia consisting essentially of transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one (finasteride) as defined by Claims 28, 29 and 31-34, the method of treating androgenic alopecia consisting essentially of transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5-alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, in a transdermal skin patch, as defined by Claims 30 and 35, and the transdermal skin patch consisting essentially of a 5-alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, as the active ingredient as defined by Claims 36 and 37, are nonobvious over the cited reference because the term "consisting essentially of" precludes additional active ingredients. Applicants submit that the Board of Appeals should reverse the Examiner's rejections of Claims 28-37. Favorable action by the Board is respectfully requested.

A. The § 103(a) Obviousness Rejection of Claims 28-31 and 34-35 over US 5,407,944 is Improper

As stated previously, Claims 28, 29 and 31-34 specify that the method of treating androgenic alopecia consists essentially of transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor, and Claims

30 and 35 depend from Claims 28 and 31, respectively, further distinguish the present invention and add the limitation that the 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, is administered via transdermal patch. US 5,407,944 to Goldman teaches a method for promoting hair growth comprising administering a therapeutically effective amount of at least two active agents. Indeed, in the only exemplification in US 5,407,944, the 5alpha-reductase 2 inhibitor is used in prophetic examples (1) with a vasodilator and estradiol, in a 3 ingredient treatment (US 5,407,944, col. 8, line 68-col. 9, line 2) and (2) with a vasodilator and a 5alpha-reductase 2 inhibitor in a 2 ingredient combination (US 5,407,944, col. 9, lines 3-4). Still further, with regard to Claims 30 and 35, US 5,407,944 does not teach or suggest administration of a 5alpha-reductase 2 inhibitor via transdermal patch. US 5,407,944 does not suggest transdermal administration of a 5alpha-reductase 2 inhibitor, particularly finasteride, as the sole active ingredient for the treatment of androgenic alopecia.

Contrary to the Examiner's contention, the expression "consisting essentially of" does not permit additional active ingredients, such as vasodilators and estradiol. "Consisting essentially of" excludes other elements from having any essential significance to the combination. The additional ingredients in US 5,407,944 useful for growing hair are elements that would have essential significance in the combination. "Consisting essentially of" permits a degree of "reading on" additional unspecified substances which do not affect the basic and novel characteristics of the claimed invention. *See*, Practicing Law Institute, *Landis On Mechanics of Patent Claim Drafting,* 1997, § 8. However, additional active ingredients, such as vasodilators and estradiol, do indeed affect the basic characteristics of the transdermal administration of a 5alpha-reductase 2 inhibitor as part of a method for treating androgenic alopecia by providing a SECOND and/or THIRD active agent for hair growth and are not encompassed by the presently drafted claims containing the term "consisting essentially of".

The aspect of the invention described in the specification encompassed by the present claims concerns 5alpha-reductase 2 inhibitors for transdermal administration and/or 5alpha-reductase 2 inhibitor transdermal patches for the treatment of androgenic alopecia. The only combination of ingredients described in the present specification is with a potassium channel opener such as minoxidil. This class of compounds is included in the class "vasodilators" in the US 5,407,944 patent. However, vasodilators are inappropriate for transdermal administration for the treatment of androgenic alopecia.

Transdermal administration generally delivers drugs systemically (bodywide). *See, e.g., The Merck Manual of Medical Information: Second Home Edition*, "Chapter 11, Drugs:

Administration and Kinetics of Drugs," revised February 1, 2003, http://www.merck.com/mmhe/print/sec02/ch011/ch011b.html, "Some drugs are delivered bodywide through a patch on the skin. . . ." Oral administration, like transdermal administration, also generally delivers products systemically (bodywide). However, minoxidil and other vasodilators are not appropriate for systemic (bodywide) administration for the treatment of androgenic alopecia, because, systemically administered, these compounds cause adverse effects including tachycardia and hypertrichosis (unwanted hair growth all over the body.) *See*, Sasson et al., "Status of Medical Treatment for Androgenic Alopecia" *International J. Dermatology*, 32(10): 701-706 (1993) at 701. The label for ROGAINE® describes the following side effects for oral administration:

> Because of its serious side effects, oral minoxidil is indicated only for the treatment of hypertension that is symptomatic or associated with target organ damage and is not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs. . . The major side effects of oral minoxidil, aside from unwelcome generalized hair growth, result from fluid retention, often profound, and tachycardia. . . Fluid retention can lead to market weight gain, local or generalized edema, heart failure, and pleural or pericardial effusion including cardiac tamponade. Pericarditis has been reported, usually in patients with renal failure or collagen vascular disease, but in some cases these causes of pericarditis do not seem to have been present. The tachycareia nad increased cardiac output caused by minoxidil can lead to exacerbation of existing angina or the onset of angina in person s with compromised coronary circulations. *Physician's Desk Reference, 50th Edition*, "ROGAINE®", Medical Economics Company, 2637-2641, 2638 (Montvale, NJ: 1996).

Minoxidil is marketed as ROGAINE®, a topical treatment for male pattern hair loss to limit these side effects.

For transdermal treatment of androgenic alopecia, Applicants have claimed a method consisting essentially of transdermally administering a 5alpha-reductase 2 inhibitor. The remaining issue presented in this appeal is whether the additional active agents "materially affect the basic and novel properties of the invention." *PPG Indus. V. Guardian Indus. Corp.*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353 (Fed. Cir 1998); *In re Janakirama-Rao*, 317 F.2d 951, 954, 137 USPQ 893, 894 (CCPA 1963).. It is Applicants' position that additional active ingredients affect the basic and novel characteristics of the transdermal administration of 5alpha-reductase 2 inhibitor as part of a method for treating androgenic alopecia by providing a SECOND and/or THIRD active agent for hair growth, and that the claims read in light of the specification by one

of ordinary skill in the art does not teach or suggest transdermal administration of finasteride together with other agents for treating androgenic alopecia.

B. The § 103 (a) Obviousness Rejection of Claims 36 and 37 over US 5,407,944 is Improper

Claims 36 and 37 are directed to a transdermal skin patch consisting essentially of a 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, as the active ingredient. US 5,407,944 does not teach or suggest a transdermal skin patch consisting essentially of a 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, as the active ingredient. In particular, the term "consisting essentially of. . . as the active ingredient" precludes the addition of other active ingredients in the composition.

US 5,407,944 does describe several formulations in the patent; namely:

(1) Minoxidil as a topical solution (col. 3, lines 39-52);
(2) Minoxidil in tablet form (col. 3, lines 53-62);
(3) Nitroglycerin as a transdermal system (col. 4, lines 1-6);
(4) Diazoxide as a capsule or suspension (col. 4, lines 7-18);
(5) Nifedipine as a capsule (col. 4, lines 19-38);
(6) Nifedipine as a controlled release tablet for oral administration (col. 4, lines 42-56);
(7) 17beta-estradiol as tablet or cream (col. 4, line 57 to col. 5,line 28);
(8) 17beta-estradiol as a transdermal patch (col. 5, lines 29-42);
(9) Finasteride as a tablet (col. 5, lines 43-62).

US 5,407,944 patent at col. 6, lines 10 to 50, does not teach a transdermal skin patch comprising a composition containing 5α-reductase 2 inhibitor (e.g., 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one), as the Examiner stated. In fact, read in context with the particular formulations US 5,407,944 teaches in the patent (cited above), US 5,407,944 teaches away from the transdermal skin patch consisting essentially of a 5alpha-reductase inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, as the active ingredient, because the only 5alpha-reductase inhibitor composition is provided as a tablet (US 5,407,944, col. 5, lines 51-58), and the prophetic "Example 2" does not describe either the dosage or mode of administration of 5alpha reductase inhibitor in groups 3 (vasodilator, estradiol, and 5alpha reductase inhibitor) or 5 (vasodilator and 5alpha reductase inhibitor) (US 5,407,944, col. 8, line 68-col. 9, line 8). Nor does "Example 2" describe any concrete results, but states that "a combined treatment of vasodilator,

estradiol and/or a 5-α-reductase inhibitor represents the optimum medical treatment for early MPB." (US 5,407,944, col. 8, lines 24-27).

CONCLUSION

Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejections of Claims 28 to 37.

Respectfully submitted,

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CLAIMS APPENDIX

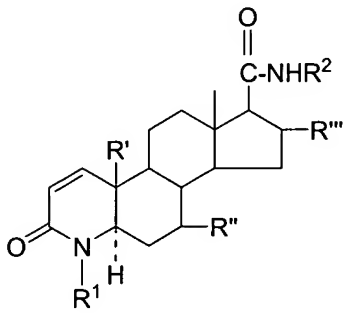
The claims on appeal are as follows:

Claim 28. A method of treating androgenic alopecia consisting essentially of transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor.

Claim 29. The method according to Claim 28, wherein androgenic alopecia is male pattern baldness.

Claim 30. The method according to Claim 28, wherein the 5alpha-reductase 2 inhibitor is transdermally administered by a transdermal skin patch.

Claim 31. The method according to Claim 28, wherein the 5alpha-reductase 2 inhibitor has the structural formula I:



I

or a pharmaceutically acceptable salt thereof wherein:

R^1 is hydrogen, methyl or ethyl;

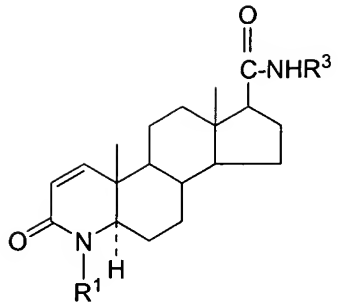
R^2 is a hydrocarbon radical selected from straight and branched chain alkyl of from 1-12 carbons or monocyclic aryl optionally containing 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents selected from Cl, F and Br;

R' is hydrogen or methyl;

R" is hydrogen or β-methyl; and

R''' is hydrogen, α-methyl or β-methyl.

Claim 32. The method according to Claim 28, wherein the 5alpha-reductase 2 inhibitor has the structural formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or methyl; and

R^3 is branched chain alkyl of from 4 to 8 carbons.

Claim 33. A method of treating androgenic alopecia consisting essentially of transdermally administering to a person in need of such treatment a therapeutically effective amount of 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one.

Claim 34. The method of Claim 33 wherein androgen alopecia is male pattern baldness.

Claim 35. The method according to Claim 33, wherein the 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one inhibitor is transdermally administered by a transdermal skin patch.

Claim 36. A transdermal skin patch consisting essentially of a therapeutically effective amount of a 5 alpha-reductase 2 inhibitor as the active ingredient.

Claim 37. The transdermal skin patch according to Claim 36 wherein the 5alpha-reductase 2 inhibitor is 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one.

EVIDENCE APPENDIX

1. The Merck Manual of Medical Information: Second Home Edition, Chapter 11, Drugs: Administration and Kinetics of Drugs, http://www.merck.com/mmhe/print/sec02/ch011/ch011b.html, revised February 1, 2003.

2. *Physician's Desk Reference, 50th Edition*, "ROGAINE®", Medical Economics Company, 2637-2641, 2638 (Montvale, NJ: 1996).

3. Sasson et al., "Status of Medical Treatment for Androgenic Alopecia" International J. Dermatology, 32(10): 701-706 (1993).

EVIDENCE 1

1. The Merck Manual of Medical Information: Second Home Edition, Chapter 11, Drugs: Administration and Kinetics of Drugs, http://www.merck.com/mmhe/print/sec02/ch011/ch011b.html, revised February 1, 2003.

THE MERCK MANUAL OF MEDICAL INFORMATION—
SECOND HOME EDITION

SECTION Drugs

SUBJECT Administration and Kinetics of Drugs

Administration

Drugs are introduced into the body by several routes. They may be taken by mouth (orally); given by injection into a vein (intravenously), into a muscle (intramuscularly), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously); placed under the tongue (sublingually); inserted in the rectum (rectally) or vagina (vaginally); instilled in the eye (by the ocular route); sprayed into the nose and absorbed through the nasal membranes (nasally); breathed into the lungs, usually through the mouth (by inhalation); applied to the skin (cutaneously) for a local (topical) or bodywide (systemic) effect; or delivered through the skin by a patch (transdermally) for a systemic effect. Each route has specific purposes, advantages, and disadvantages.

Oral Route Because the oral route is the most convenient and usually the safest and least expensive, it is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach, but usually, most of the drug is absorbed from the small intestine. The drug passes through the intestinal wall and then the liver before it is transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount reaching the bloodstream. Consequently, for the same effect, such drugs are often given in smaller doses when they are injected directly into the bloodstream (intravenously).

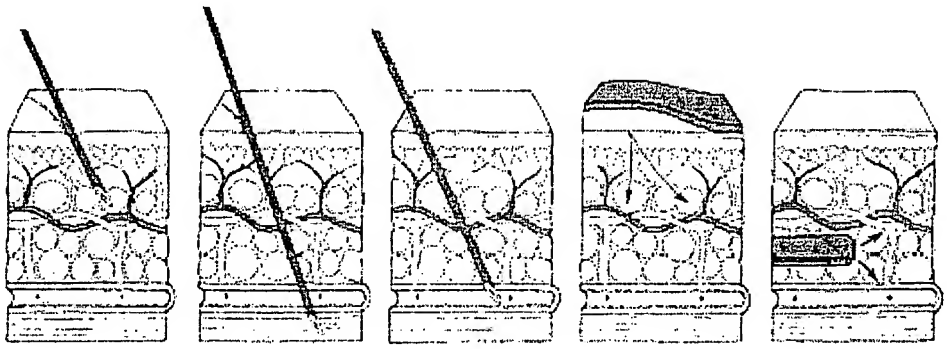
When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain other drugs, and still others cannot be taken orally at all.

Some orally administered drugs irritate the digestive tract; for example, aspirin and most other nonsteroidal anti-inflammatory drugs (see Pain: Nonsteroidal Anti-Inflammatory Drugs) can harm the lining of the stomach and small intestine and can cause or aggravate preexisting ulcers (see Peptic Disorders: Causes). Other drugs are absorbed poorly or erratically in the digestive tract or are destroyed by the acid and digestive enzymes in the stomach.

Other routes are usually used only when the oral route cannot be used: for example, when a person cannot take anything by mouth, when a drug must be administered rapidly or in a precise or very high dose, or when a drug is poorly or erratically absorbed from the digestive tract.

Injection Routes Administration by injection (parenteral administration) includes the subcutaneous, intramuscular, intravenous, and intrathecal routes. A drug product can be prepared or manufactured in ways that prolong drug absorption from the injection site for hours, days, or longer; such products do not need to be administered as often as drug products with more rapid absorption.

Through the Skin



Sometimes a drug is given through the skin—by needle (subcutaneous, intramuscular, or intravenous route), by patch (transdermal route), or by implantation.

For the subcutaneous route, a needle is inserted into fatty tissue just beneath the skin. The drug is injected, then moves into small blood vessels (capillaries) and is carried away by the bloodstream or reaches the bloodstream through the lymphatic vessels. Protein drugs that are large in size, such as insulin, usually reach the bloodstream through the lymphatic vessels because these drugs move slowly from the tissues into capillaries. The subcutaneous route is used for many protein drugs because such drugs would be digested in the digestive tract if they were taken orally.

Certain drugs (such as progestin, used for birth control (see Family Planning: Contraceptive Implants) may be given by inserting plastic capsules under the skin (subcutaneously). This route is rarely used.

The intramuscular route is preferred to the subcutaneous route when larger volumes of a drug product are needed. Because the muscles lie below the skin and fatty tissues, a longer needle is used. Drugs are usually injected into muscle in the upper arm, thigh, or buttock. How quickly the drug is absorbed into the bloodstream depends, in part, on the blood supply to the muscle: The sparser the blood supply, the longer the drug takes to be absorbed. The blood supply is increased during physical activity.

For the intravenous route, a needle is inserted directly into a vein. A solution containing the drug may be given in a single dose or by continuous infusion. For infusion, the solution is moved by gravity (from a collapsible plastic bag) or by an infusion pump through thin flexible tubing to a tube (catheter) inserted in a vein, usually in the forearm. Intravenous administration is the best way to deliver a precise dose quickly and in a well-controlled manner throughout the body. It is also used for irritating solutions, which, if given by subcutaneous or intramuscular injection, would cause pain and tissue damage. An intravenous injection can be more difficult to administer than a subcutaneous or intramuscular injection, because inserting a needle or catheter into a vein may be difficult, especially if people are obese.

When given intravenously, a drug is immediately delivered to the bloodstream and tends to take effect more quickly than when given by any other route. Consequently, doctors closely monitor patients who receive an intravenous injection for signs that the drug is working or is causing undesired side effects. Also, the effect of a drug given by this route tends to last for a shorter time.

For the intrathecal route, a needle is inserted between two vertebrae in the lower spine and into the space around the spinal cord. The drug is then injected into the spinal canal. A small amount of local anesthetic is often used to numb the injection site. This route is used when a drug is needed to produce rapid or local effects on the brain, spinal cord, or the layers of tissue covering them (meninges)—for example, to treat infections of these structures. Anesthetics are sometimes

given this way.

Sublingual Route A few drugs are placed under the tongue (taken sublingually) so that they can be absorbed directly into the small blood vessels that lie beneath the tongue. The sublingual route is especially good for nitroglycerin—which is used to relieve angina (chest pain due to an inadequate blood supply to the heart muscle)—because absorption is rapid and the drug immediately enters the bloodstream without first passing through the intestinal wall and liver. However, most drugs cannot be taken this way because they may be absorbed incompletely or erratically.

Rectal Route Many drugs that are administered orally can also be administered rectally as a suppository. In this form, a drug is mixed with a waxy substance that dissolves or liquefies after it is inserted into the rectum. Because the rectum's wall is thin and its blood supply rich, the drug is readily absorbed. A suppository is prescribed for people who cannot take a drug orally because they have nausea, cannot swallow, or have restrictions on eating, as is required after many surgical operations. Drugs that are irritating in suppository form may have to be given by injection.

Vaginal Route Some drugs may be administered vaginally to women as a solution, tablet, cream, gel, or suppository. The drug is slowly absorbed through the vaginal wall. This route is often used to give estrogen to women at menopause, because the drug helps prevent thinning of the vaginal wall, an effect of menopause (see Menopause: Hormone Therapy).

Ocular Route Drugs used to treat eye disorders (such as glaucoma, conjunctivitis, herpes simplex infection, and injuries) can be mixed with inactive substances to make a liquid, gel, or ointment, so that they can be applied to the eye. Liquid eye drops are relatively easy to use but may run off the eye too quickly to be absorbed well. Gel and ointment formulations keep the drug in contact with the eye surface longer. Solid inserts, which release the drug continuously and in slow amounts, are also available, but they may be hard to put and keep in place. Ocular drugs are almost always used for their local effects. For example, artificial tears are used to relieve dry eyes. Other drugs (for example, those used to treat glaucoma (see Drugs Used to Treat Glaucoma), such as acetazolamide and betaxolol and those used to dilate pupils, such as phenylephrine and tropicamide) produce a local effect after they are absorbed through the cornea and conjunctiva. Some of these drugs then enter the bloodstream and may have unwanted effects on other parts of the body.

Nasal Route If a drug is to be breathed in and absorbed through the thin mucous membrane that lines the nasal passages, it must be transformed into tiny droplets in air (atomized). Once absorbed, the drug enters the bloodstream. Drugs taken by this route generally work quickly. Some of them irritate the nasal passages. Drugs that can be taken by the nasal route include nicotine (for smoking cessation), calcitonin (for osteoporosis), dihydroergotamine (for migraine headaches), and corticosteroids (for allergies and asthma).

Inhalation Gases used for general anesthesia, such as nitrous oxide, are given by inhalation. Drugs given by inhalation through the mouth must be atomized into smaller particles than those given by the nasal route, so that the drug can pass through the windpipe (trachea) and into the lungs. How deeply into the lungs they go depends on the size of the droplets; smaller droplets go deeper. Inside the lungs, they are absorbed into the bloodstream. Relatively few drugs are taken this way because inhalation must be carefully monitored to ensure that a person receives the right amount of drug within a specified time. Usually, this method is used to administer drugs that act on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers.

Cutaneous Route Drugs applied to the skin are usually used for their local effects and thus are most commonly used to treat superficial skin disorders, such as psoriasis, eczema, skin infections (viral, bacterial, and fungal), itching, and dry skin. The

Drug Administration by Inhalation

drug is mixed with inactive substances. Depending on the consistency of the inactive substances, the formulation may be an ointment, a cream, a lotion, a solution, a powder, or a gel (see Diagnosis and Treatment of Skin Disorders: Topical Preparations).

Transdermal Route Some drugs are delivered bodywide through a patch on the skin. These drugs, sometimes mixed with a chemical (such as alcohol) that enhances penetration of the skin, pass through the skin to the bloodstream without injection. Through a patch, the drug can be delivered slowly and continuously for many hours or days or even longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particular useful for drugs that are quickly eliminated from the body, because such drugs, if taken in other forms, would have to be taken frequently. However, patches may irritate the skin of some people. In addition, patches are limited by how quickly the drug can penetrate the skin. Only drugs to be given in relatively small daily doses can be given through patches. Examples of such drugs include nitroglycerin (for angina), scopolamine (for motion sickness), nicotine (for smoking cessation), clonidine (for high blood pressure), and fentanyl (for pain relief).

Last reviewed/revised February 1, 2003

Transdermal Drug Administration

EVIDENCE 2

2. *Physician's Desk Reference, 50th Edition*, "ROGAINE®", Medical Economics Company, 2637-2641, 2638 (Montvale, NJ: 1996).

PHYSICIANS' DESK REFERENCE®

Medical Consultant
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President and Chief Operating Officer, Drug Information Services Group: Thomas F. Rice

Director of Product Management: Stephen B. Greenberg
Associate Product Managers: Cy S. Caine, Howard N. Kanter
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MEDICAL ECONOMICS

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Under the federal Food, Drug & Cosmetics (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer for only those uses for which the drug's safety and effectiveness have been established. The Code of Federal Regulations 201.100(d)(1) pertaining to labeling for prescription products requires that for PDR content "indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions" must be *"same in language and emphasis"* as the approved labeling for the products. FDA regards the words *same in language and emphasis* as requiring VERBATIM use of the approved labeling providing such information. Furthermore, information that is emphasized in the approved labeling by the use of type set in a box, or in capitals, boldface, or italics, must be given the same emphasis in PDR.

The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling. For products that do not have official package circulars, the publisher has emphasized the necessity of describing such products comprehensively, so that physicians can have access to all information essential for intelligent and informed decision making.

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Upjohn—Cont.

arterial pressure fall significantly, decrease the rate of infusion immediately.

In infants with restricted pulmonary blood flow, measure efficacy of PROSTIN VR PEDIATRIC by monitoring improvement in blood oxygenation. In infants with restricted systemic blood flow, measure efficacy by monitoring improvement of systemic blood pressure and blood pH.

Drug Interactions: No drug interactions have been reported between PROSTIN VR PEDIATRIC and the therapy standard in neonates with restricted pulmonary or systemic blood flow. Standard therapy includes antibiotics, such as penicillin and gentamicin; vasopressors, such as dopamine and isoproterenol; cardiac glycosides; and diuretics, such as furosemide.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term carcinogenicity studies and fertility studies have not been done. The Ames and Alkaline Elution assays reveal no potential for mutagenesis.

ADVERSE REACTIONS

Central Nervous System

Apnea has been reported in about 12% of the neonates treated. (See WARNING box.) Other common adverse reactions reported have been fever in about 14% of the patients treated and seizures in about 4%. The following reactions have been reported in less than 1% of the patients: cerebral bleeding, hyperextension of the neck, hyperirritability, hypothermia, jitteriness, lethargy, and stiffness.

Cardiovascular System

The most common adverse reactions reported have been flushing in about 10% of patients (more common after intraarterial dosing), bradycardia in about 7%, hypotension in about 4%, tachycardia in about 3%, cardiac arrest in about 1%, and edema in about 1%. The following reactions have been reported in less than 1% of the patients: congestive heart failure, hyperemia, second degree heart block, shock, spasm of the right ventricle infundibulum, supraventricular tachycardia, and ventricular fibrillation.

Respiratory System

The following reactions have been reported in less than 1% of the patients: bradypnea, bronchial wheezing, hypercapnia, respiratory depression, respiratory distress, and tachypnea.

Gastrointestinal System

See WARNINGS

The most common adverse reaction reported has been diarrhea in about 2% of the patients. The following reactions have been reported in less than 1% of the patients: gastric regurgitation, and hyperbilirubinemia.

Hematologic System

The most common hematologic event reported has been disseminated intravascular coagulation in about 1% of the patients. The following events have been reported in less than 1% of the patients: anemia, bleeding, and thrombocytopenia.

Excretory System

Anuria and hematuria have been reported in less than 1% of the patients.

Skeletal System

Cortical proliferation of the long bones has been reported. See PRECAUTIONS.

Miscellaneous

Sepsis has been reported in about 2% of the patients. Peritonitis has been reported in less than 1% of the patients. Hypokalemia has been reported in about 1%, and hypoglycemia and hyperkalemia have been reported in less than 1% of the patients.

OVERDOSAGE

Apnea, bradycardia, pyrexia, hypotension, and flushing may be signs of drug overdosage. If apnea or bradycardia occurs, discontinue the infusion, and provide appropriate medical treatment. Caution should be used in restarting the infusion. If pyrexia or hypotension occurs, reduce the infusion rate until these symptoms subside. Flushing is usually a result of incorrect intraarterial catheter placement, and the catheter should be repositioned.

DOSAGE AND ADMINISTRATION

The preferred route of administration for PROSTIN VR PEDIATRIC Sterile Solution is continuous intravenous infusion into a large vein. Alternatively, PROSTIN VR PEDIATRIC may be administered through an umbilical artery catheter placed at the ductal opening. Increases in blood pO_2 (torr) have been the same in neonates who received the drug by either route of administration.

Begin infusion with 0.05 to 0.1 micrograms alprostadil per kilogram of body weight per minute. A starting dose of 0.1 micrograms per kilogram of body weight per minute is the recommended starting dose based on clinical studies; however, adequate clinical response has been reported using a starting dose of 0.05 micrograms per kilogram of body weight per minute. After a therapeutic response is achieved (increased pO_2 in infants with restricted pulmonary blood flow or increased systemic blood pressure and blood pH in infants with restricted systemic blood flow), reduce the infusion rate to provide the lowest possible dosage that maintains the response. This may be accomplished by reducing the dosage from 0.1 to 0.05 to 0.025 to 0.01 micrograms per kilogram of body weight per minute. If response to 0.05 micrograms per kilogram of body weight per minute is inadequate, dosage can be increased up to 0.4 micrograms per kilogram of body weight per minute although, in general, higher infusion rates do not produce greater effects.

Dilution Instructions: To prepare infusion solutions, dilute 1 mL of PROSTIN VR PEDIATRIC Sterile Solution with Sodium Chloride Injection USP or Dextrose Injection USP. Undiluted PROSTIN VR PEDIATRIC Sterile Solution may interact with the plastic sidewalls of volumetric infusion chambers causing a change in the appearance of the chamber and creating a hazy solution. Should this occur, the solution and the volumetric infusion chamber should be replaced.

When using a volumetric infusion chamber, the appropriate amount of intravenous infusion solution should be added to the chamber first. The undiluted PROSTIN VR PEDIATRIC Sterile Solution should then be added to the intravenous infusion solution, avoiding direct contact of the undiluted solution with the walls of the volumetric infusion chamber. Dilute to volumes appropriate for the pump delivery system available. Prepare fresh infusion solutions every 24 hours. *Discard any solution more than 24 hours old.*

Sample Dilutions and Infusion Rates to Provide a Dosage of 0.1 Micrograms per Kilogram of Body Weight per Minute

Add 1 ampoule (500 micrograms) alprostadil to:	Approximate Concentration of resulting solution (micrograms/mL)	Infusion rate (mL/min per kg of body weight)
250 mL	2	0.05
100 mL	5	0.02
50 mL	10	0.01
25 mL	20	0.005

Example: To provide 0.1 micrograms/kilogram of body weight per minute to an infant weighing 2.8 kilograms using a solution of 1 ampoule PROSTIN VR PEDIATRIC in 100 mL of saline or dextrose: INFUSION RATE = 0.02 mL/min per kg × 2.8 kg = 0.056 mL/min or 3.36 mL/hr.

HOW SUPPLIED

PROSTIN VR PEDIATRIC Sterile Solution is available in packages of 5—1 mL ampoules (NDC 0009-3169-01) and as a package of 5 × 1 mL ampoules (NDC 0009-3169-06). Each mL contains 500 micrograms alprostadil in dehydrated alcohol. Store PROSTIN VR PEDIATRIC Sterile Solution in a refrigerator at 2° to 8° C (36° to 46° F).

Caution: Federal law prohibits dispensing without prescription.

Revised January 1995 811 987 010
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PROVERA® Ⓡ
brand of medroxyprogesterone acetate tablets, USP

WARNING

THE USE OF PROVERA (MEDROXYPROGESTERONE ACETATE) DURING THE FIRST FOUR MONTHS OF PREGNANCY IS NOT RECOMMENDED.

Progestational agents have been used beginning with the first trimester of pregnancy in an attempt to prevent habitual abortion. There is no adequate evidence that such use is effective when such drugs are given during the first four months of pregnancy. Furthermore, in the vast majority of women, the cause of abortion is a defective ovum, which progestational agents could not be expected to influence. In addition, the use of progestational agents, with their uterine-relaxant properties, in patients with fertilized defective ova may cause a delay in spontaneous abortion. Therefore, the use of such drugs during the first four months of pregnancy is not recommended.

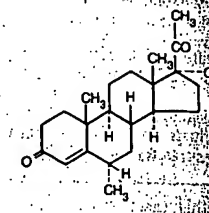
Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as so[me] induce mild virilization of the externa[l] female fetus, and because of the increa[se] hypospadias in the male fetus, it is pru[dent] use of these drugs during the first t[rimester] nancy.

If the patient is exposed to PROVE[RA] droxyprogesterone acetate) during the [first] of pregnancy or if she becomes pregn[ant] this drug, she should be apprised of the [risk to] the fetus.

DESCRIPTION

PROVERA Tablets contain medroxypr[ogesterone] which is a derivative of progesterone. [It is a] white, odorless crystalline powder, sta[ble] between 200 and 210° C. It is freely sol[uble] soluble in acetone and in dioxane, sparin[gly] hol and in methanol, slightly soluble in e[ther] in water.

The chemical name for medroxyproge[sterone] Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-[methyl-], structural formula is:



Each PROVERA tablet for oral adminis[tration] mg, 5 mg or 10 mg of medroxyprogesterone [acetate]. ingredients: calcium stearate, corn starch, [mineral] oil, sorbic acid, sucrose, talc. The 2.5 mg [tablet] FD&C Yellow no. 6.

ACTIONS

Medroxyprogesterone acetate, administered [orally] terally in the recommended doses to wo[men] endogenous estrogen, transforms prolifer[ative] endometrium. Androgenic and anabolic [activity] noted; but the drug is apparently devoid of [estrogenic] genic activity. While parenterally adm[inistered] progesterone acetate inhibits gonado[trophin] which in turn prevents follicular matura[tion]. available data indicate that this does [not occur] usually recommended oral dosage is g[reater than] doses.

INDICATIONS AND USAGE

Secondary amenorrhea; abnormal uteri[ne] hormonal imbalance in the absence of [organic] such as fibroids or uterine cancer.

CONTRAINDICATIONS

1. Thrombophlebitis, thromboembolic [disorders], apoplexy or patients with a past [history of] conditions.
2. Liver dysfunction or disease.
3. Known or suspected malignancy of [the] organs.
4. Undiagnosed vaginal bleeding.
5. Missed abortion.
6. As a diagnostic test for pregnancy.
7. Known sensitivity to PROVERA Tab[lets].

WARNINGS

1. The physician should be alert to the [possibility] tions of thrombotic disorders (thrombophlebitis [and] cular disorders, pulmonary embolism, and [cerebral] sis). Should any of these occur or be [suspected], should be discontinued immediately.
2. Beagle dogs treated with medroxyp[rogesterone] developed mammary nodules some of wh[ich] Although nodules occasionally appeared in [control] they were intermittent in nature, whereas [the] drug-treated animals were larger, more [numerous] tent, and there were some breast malignan[cies] ses. Their significance with respect to hu[man risk] established.
3. Discontinue medication pending exa[mination] sudden partial or complete loss of vision, [or] den onset of proptosis, diplopia or migra[ine] reveals papilledema or retinal vascular [lesions] should be withdrawn.
4. Detectable amounts of progestin hav[e been] the milk of mothers receiving the drug. [Caution] the nursing infant has not been determ[ined].
5. Usage in pregnancy is not recommen[ded] Box).
6. Retrospective studies of morbidity an[d mortality] Britain and studies of morbidity in the

...istically significant association between thrombosis and the use of oral contraceptives.[1-4] The estimated relative risk of thromboembolism in the study by Doll[3] was about sevenfold, while Sartwell and ... in the United States found a relative risk of 4.4, ...that the users are several times as likely to undergo ...bolic disease without evident cause as nonusers. ...can study also indicated that the risk did not per... discontinuation of administration, and that it was ...ed by long continued administration. The Ameri... was not designed to evaluate a difference between ...

...TIONS

...treatment physical examination should include ...reference to breast and pelvic organs, as well as ...nicolaou smear.

...progestogens may cause some degree of fluid ...tion, conditions which might be influenced by this ...such as epilepsy, migraine, asthma, cardiac or ...dysfunction, require careful observation.

...of breakthrough bleeding, as in all cases of irreg...leeding per vaginum, nonfunctional causes should ...e in mind. In cases of undiagnosed vaginal bleed... adequate diagnostic measures are indicated.

...ts who have a history of psychic depression should ...fully observed and the drug discontinued if the ...sion recurs to a serious degree.

...possible influence of prolonged progestin therapy ...itary, ovarian, adrenal, hepatic or uterine func... awaits further study.

...ease in glucose tolerance has been observed in a ...percentage of patients on estrogen-progestin com... drugs. The mechanism of this decrease is ob... For this reason, diabetic patients should be care... observed while receiving progestin therapy.

...ce of the patient constitutes no absolute limiting ...although treatment with progestins may mask the ...of the climacteric.

...thologist should be advised of progestin therapy ...relevant specimens are submitted.

...e of the occasional occurrence of thrombotic disor... (thrombophlebitis, pulmonary embolism, retinal ...osis, and cerebrovascular disorders) in patients ...estrogen-progestin combinations and since the ...anism is obscure, the physician should be alert to ...rliest manifestation of these disorders.

...e of the addition of a progestin product to an estro... replacement regimen for seven or more days of a ...estrogen administration have reported a lowered ...ce of endometrial hyperplasia. Morphological ...mochemical studies of endometrium suggest that ...days of a progestin are needed to provide maximal ...ation of the endometrium and to eliminate any ...plastic changes. Whether this will provide protec... from endometrial carcinoma has not been clearly ...med. There are possible additional risks which ...e associated with the inclusion of progestin in es... replacement regimen. The potential risks include ...e effects on carbohydrate and lipid metabolism. ...age used may be important in minimizing these ...e effects.

...oglutethimide administered concomitantly with ...ERA may significantly depress the bioavailability ...OVERA.

...esis, Mutagenesis, Impairment of Fertility.

...n intramuscular administration of PROVERA has ...n to produce mammary tumors in beagle dogs (see ...S). There was no evidence of a carcinogenic effect ...with the oral administration of PROVERA to rats ...Medroxyprogesterone acetate was not mutagenic ...of *in vitro* or *in vivo* genetic toxicity assays. ...ogesterone acetate at high doses is an antifertility ...igh doses would be expected to impair fertility ...ssation of treatment.

...n for the Patient

...l information at the end of insert.

...E REACTIONS

...(See WARNING Box for possible adverse effects ...

...reast tenderness or galactorrhea has been re... ...

...ivity reactions consisting of urticaria, pruritus, ...generalized rash have occurred in an occasional ...e, alopecia and hirsutism have been reported in ...

...bolic Phenomena—Thromboembolic phenom...ing thrombophlebitis and pulmonary embolism ...reported.

...ing adverse reactions have been observed in ...ng progestins including PROVERA Tablets:

...ugh bleeding

...n menstrual flow

amenorrhea
edema
change in weight (increase or decrease)
changes in cervical erosion and cervical secretions
cholestatic jaundice
anaphylactoid reactions and anaphylaxis
rash (allergic) with and without pruritus
mental depression
pyrexia
insomnia
nausea
somnolence

A statistically significant association has been demonstrated between use of estrogen-progestin combination drugs and the following serious adverse reactions: thrombophlebitis; pulmonary embolism and cerebral thrombosis and embolism. For this reason patients on progestin therapy should be carefully observed.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions:

neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs:

rise in blood pressure in susceptible individuals
premenstrual-like syndrome
changes in libido
changes in appetite
cystitis-like syndrome
headache
nervousness
fatigue
backache
hirsutism
loss of scalp hair
erythema multiforme
erythema nodosum
hemorrhagic eruption
itching
dizziness

In view of these observations, patients on progestin therapy should be carefully observed.

The following laboratory results may be altered by the use of estrogen-progestin combination drugs:

Increased sulfobromophthalein retention and other hepatic function tests.

Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.

Metyrapone test.

Pregnanediol determination.

Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T^3 uptake values.

DOSAGE AND ADMINISTRATION

Secondary Amenorrhea—PROVERA Tablets may be given in dosages of 5 to 10 mg daily for from 5 to 10 days. A dose for inducing an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen is 10 mg of PROVERA daily for 10 days. In cases of secondary amenorrhea, therapy may be started at any time. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing PROVERA therapy.

Abnormal Uterine Bleeding Due to Hormonal Imbalance in the Absence of Organic Pathology—Beginning on the calculated 16th or 21st day of the menstrual cycle, 5 to 10 mg of medroxyprogesterone acetate may be given daily for from 5 to 10 days. To produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen, 10 mg of medroxyprogesterone acetate daily for 10 days beginning on the 16th day of the cycle is suggested. Progestin withdrawal bleeding usually occurs within three to seven days after discontinuing therapy with PROVERA. Patients with a past history of recurrent episodes of abnormal uterine bleeding may benefit from planned menstrual cycling with PROVERA.

HOW SUPPLIED

PROVERA Tablets are available in the following strengths and package sizes:

2.5 mg (scored, round, orange)		
	Bottles of 30	NDC 0009-0064-06
	Bottles of 100	NDC 0009-0064-04
5 mg (scored, hexagonal, white)		
	Bottles of 30	NDC 0009-0286-32
	Bottles of 100	NDC 0009-0286-03
10 mg (scored, round, white)		
	Bottles of 30	NDC 0009-0050-09
	Bottles of 100	NDC 0009-0050-02
	Bottles of 500	NDC 0009-0050-11
	DOSEPAK™ Unit of Use (10)	NDC 0009-0050-12

Store at controlled room temperature 15°–30°C (59°–86°F).

REFERENCES

1. Royal College of General Practitioners: Oral contraception and thromboembolic disease. J Coll Gen Pract 13:267–279, 1967.
2. Inman WHW, Vessey MP: Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. Br Med J 2:193–199, 1968.
3. Vessey MP, Doll R: Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J 2:651–657, 1969.
4. Sartwell PE, Masi AT, Arthes FG, et al: Thromboembolism and oral contraceptives: An epidemiological case-control study. Am J Epidemiol 90:365–380, 1969.

The text of the patient insert for progesterone and progesterone-like drugs is set forth below.

PATIENT INFORMATION

PROVERA Tablets contain medroxyprogesterone acetate a progesterone. The information below is that which the U.S. Food and Drug Administration requires be provided for all patients taking progesterones. The information below relates only to the risk to the unborn child associated with use of progesterone during pregnancy. For further information on the use, side effects and other risks associated with this product, ask your doctor.

WARNING FOR WOMEN

Progesterone or progesterone-like drugs have been used to prevent miscarriage in the first few months of pregnancy. No adequate evidence is available to show that they are effective for this purpose. Furthermore, most cases of early miscarriage are due to causes which could not be helped by these drugs.

There is an increased risk of minor birth defects in children whose mothers take this drug during the first 4 months of pregnancy. Several reports suggest an association between mothers who take these drugs in the first trimester of pregnancy and genital abnormalities in male and female babies. The risk to the male baby is the possibility of being born with a condition in which the opening of the penis is on the underside rather than the tip of the penis (hypospadias). Hypospadias occurs in about 5 to 8 per 1,000 male births and is about doubled with exposure to these drugs. There is not enough information to quantify the risk to exposed female fetuses, but enlargement of the clitoris and fusion of the labia may occur, although rarely.

Therefore, since drugs of this type may induce mild masculinization of the external genitalia of the female fetus, as well as hypospadias in the male fetus, it is wise to avoid using the drug during the first trimester of pregnancy.

These drugs have been used as a test for pregnancy but such use is no longer considered safe because of possible damage to a developing baby. Also, more rapid methods for testing for pregnancy are now available.

If you take PROVERA and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible.

Caution: Federal law prohibits dispensing without prescription.

Revised January 1992 812 584 409
691015

Shown in Product Identification Guide, page 338

ROGAINE®

brand of minoxidil topical solution
2%
For Topical Use

DESCRIPTION

ROGAINE Topical Solution is a hair growth stimulant. ROGAINE contains the active ingredient minoxidil. Minoxidil appears as a white or off-white, odorless crystalline solid that is soluble in water to the extent of approximately 2 mg/mL, is readily soluble in propylene glycol or ethanol, and is almost insoluble in acetone, chloroform or ethyl acetate. The chemical name for minoxidil is 2,4-pyrimidinediamine, 6-(1-piperidinyl)-, 3-oxide (MW = 209.25). The structural formula is represented below:

[See chemical structure at top of next column.]

ROGAINE Topical Solution is available at a concentration of 2% (20 mg minoxidil per milliliter) in a solution of alcohol 60% v/v, propylene glycol, and water.

CLINICAL PHARMACOLOGY

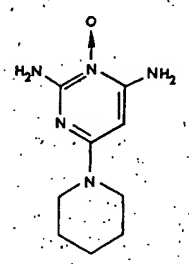
Pharmacologic Properties and Pharmacokinetics

ROGAINE Topical Solution stimulates hair growth in individuals with androgenetic alopecia, expressed in males as

Continued on next page

Information on these Upjohn products is based on labeling in effect June 1, 1995. Further information concerning these and other Upjohn products may be obtained by direct inquiry to Medical Information, The Upjohn Company, Kalamazoo, Michigan 49001.

Upjohn—Cont.



baldness of the vertex of the scalp and in females as diffuse hair loss or thinning of the frontoparietal areas. The mechanism by which minoxidil stimulates hair growth is not known but like minoxidil some other arterial dilating drugs also stimulate hair growth when given systemically.

Because of its serious side effects oral minoxidil is indicated only for the treatment of hypertension that is symptomatic or associated with target organ damage and is not manageable with maximum therapeutic doses of a diuretic plus two other antihypertensive drugs. It is a direct acting peripheral arterial dilator that reduces blood pressure by decreasing peripheral vascular resistance. Reduction of peripheral arteriolar resistance and the resulting fall in blood pressure trigger sympathetic, vagal inhibitory, and renal homeostatic mechanisms, including increased renin secretion, that lead to increased heart rate and cardiac output and salt and water retention.

The major side effects of oral minoxidil, aside from unwelcome generalized hair growth, result from fluid retention, often profound, and tachycardia, and require that minoxidil be administered in most cases with a beta-blocker or other agent to reduce heart rate and a diuretic, almost always a high ceiling (loop) diuretic. Fluid retention can lead to marked weight gain, local or generalized edema, heart failure, and pleural or pericardial effusion, including cardiac tamponade. Pericarditis has been reported, usually in patients with renal failure or collagen vascular disease, but in some cases these causes of pericarditis do not seem to have been present. The tachycardia and increased cardiac output caused by minoxidil can lead to exacerbation of existing angina or the onset of angina in persons with compromised coronary circulation. It is these serious side effects that have restricted use of oral minoxidil to patients with severe hypertension not controllable with other agents.

In placebo controlled trials involving over 3500 male patients given topical minoxidil for 4 months (longer treatment was given after the placebo group was discontinued) and in over 300 female patients given topical minoxidil for eight months, the typical systemic effects of oral minoxidil (weight gain, edema, tachycardia, fall in blood pressure, and their more serious consequences) were not seen more frequently in patients given topical minoxidil than in those given topical placebo (See ADVERSE REACTIONS). The mean changes from baseline in weight, heart rate, and blood pressure in the treated and placebo groups were similar, and the number of patients experiencing significant changes, such as a blood pressure decrease of 15 mmHg or more diastolic or 30 mmHg or more systolic, a heart rate increase of 15 beats/minute or more, or weight gain of at least 5 pounds, was also similar.

In an effort to explore the potential for systemic effects of topical minoxidil, three concentrations of topical minoxidil (1, 2 and 5%) applied twice daily were compared to low oral doses (2.5 and 5 mg given once daily), and placebo in hypertensive patients (normotensive patients have little or no blood pressure response to minoxidil at dose of 10 mg per day) in a double-blind controlled trial. The 5 mg oral dose had readily detectable effects, a fall in diastolic pressure of about 5 mmHg and an increase in heart rate of 7 beats/minute. No other group had a clear effect, although there was some evidence of a weak and inconsistent effect in the 2.5 mg oral, and possibly the 5% topical, treatments.

The failure to detect evidence of systemic effects during treatment with topical minoxidil reflects the poor absorption of topical minoxidil, which averages about 1.4% (range 0.3 to 4.5%) from normal intact scalp, and was about 2% in the hypertensive patients, whose scalps were shaved.

In a comparison of topical and oral absorption, peak serum levels of unchanged minoxidil after 1 mL b.i.d. of 2% minoxidil solution (the maximum recommended dose) averaged 5.8% (range 1.4% to 12.7%) of the level observed after 2.5 mg b.i.d. oral doses (5 mg is the recommended starting dose of oral minoxidil). Similarly, in the hypertension study, where patients had shaved scalps, mean minoxidil concentrations after 1 mL b.i.d. of 2% topical minoxidil (1.7 ng/mL) were 1/20 the concentrations seen after daily oral doses of 2.5 mg (32.8 ng/mL) or 5 mg (59.2 ng/mL). Blood levels obtained in the large controlled hair growth trials averaged less than 2 ng/mL for the 2% solution. There were, however, occasional values that were higher; about 1% of the patients on 2% minoxidil had serum levels of 5 ng/mL or greater and a few approached 30 ng/mL. It is possible, therefore, that if more than the recommended dose were applied to inflamed skin in an individual with relatively high absorption, blood levels with systemic effects might rarely be obtained. Physicians and patients need to be aware of the possibility.

Serum minoxidil levels resulting from administration of ROGAINE are governed by the drug's percutaneous absorption rate. Following cessation of topical dosing of ROGAINE approximately 95% of systemically absorbed minoxidil is eliminated within four days. The metabolic biotransformation of minoxidil absorbed following administration of ROGAINE has not been fully determined.

Minoxidil absorbed following oral administration is metabolized predominantly by conjugation with glucuronic acid at the N-oxide position in the pyrimidine ring but also by conversion to more polar products. Known metabolites exert much less pharmacologic effect than the parent compound. Minoxidil and its metabolites are excreted principally in the urine. Minoxidil does not bind to plasma proteins and its renal clearance corresponds to the glomerular filtration rate. Minoxidil does not enter the central nervous system (CNS) of experimental animals in significant amounts and it does not affect CNS function in man.

Cardiac Lesions in Animals

Minoxidil produces several cardiac lesions (described below) in animals. Some are characteristic of agents that cause tachycardia and diastolic hypotension (beta-agonists like isoproterenol, arterial dilators like hydralazine) while others are produced by a narrower range of agents with arterial dilating properties. The significance of these lesions for humans is not clear, as they have not been recognized in patients treated with oral minoxidil at systemically active doses, despite formal review of autopsies of over 150 treated patients.

- Papillary muscle/subendocardial necrosis
  The most characteristic lesion of minoxidil, seen in rat, dog, and minipig (but not monkeys) is focal necrosis of the papillary muscle and subendocardial areas of the left ventricle. These lesions appear rapidly, within a few days of treatment with doses of 0.5 to 10 mg/kg/day in the dog and minipig, and are not progressive, although they leave residual scars. They are similar to lesions produced by other peripheral arterial dilators, by theobromine, and by beta-adrenergic receptor agonists such as isoproterenol, epinephrine, and albuterol. The lesions are thought to reflect ischemia provoked by increased oxygen demand (tachycardia, increased cardiac output) and relative decrease in coronary flow (decreased diastolic pressure and decreased time in diastole) caused by the vasodilatory effects of these agents coupled with reflex or directly induced tachycardia.
- Hemorrhagic lesions
  After acute oral minoxidil treatment (0.5 to 10 mg/kg/day) in dogs and minipigs, hemorrhagic lesions are seen in many parts of the heart, mainly in the epicardium, endocardium, and walls of small coronary arteries and arterioles. In minipigs the lesions occur primarily in the left atrium while in dogs they are most prominent in the right atrium, frequently appearing as grossly visible hemorrhagic lesions. With exposure of 1–20 mg/kg/day in the dog for 30 days or longer, there is replacement of myocardial cells by proliferating fibroblasts and angioblasts, hemorrhage and hemosiderin accumulation. These lesions can be produced by topical minoxidil administration that gives systemic absorption of 0.5 to 1 mg/kg/day. Other peripheral dilators, including an experimental agent, nicorandil, and theobromine, have produced similar lesions.
- Epicarditis
  A less fully studied lesion is focal epicarditis, seen in dogs after 2 days of oral minoxidil. More recently, chronic proliferative epicarditis was observed in dogs treated topically twice a day for 90 days. In a one year oral dog study, serosanguineous percardial fluid was seen.
- Hypertrophy and Dilation
  Oral and topical studies in rats, dogs, monkeys (oral only), and rabbits (dermal only) show cardiac hypertrophy and dilation. This is presumed to represent the consequences of prolonged fluid overload; there is preliminary evidence in monkeys that diuretics partly reverse these effects.

Autopsies of over 150 patients who died of various causes after receiving oral minoxidil for hypertension have not revealed the characteristic hemorrhagic (especially atrial) lesions seen in dogs and minipigs. While areas of papillary muscle and subendocardial necrosis were occasionally seen, they occurred in the presence of known pre-existing coronary artery disease and were also seen in patients never exposed to minoxidil in another series using similar, but not identical, autopsy methods.

CLINICAL TRIAL EXPERIENCE—MALES

In clinical trials in males, three main parameters of efficacy were used: hair counts in a one inch diameter circle on the vertex of the scalp; investigator evaluation of terminal hair regrowth; and patient evaluation of hair regrowth. At the end of the 4-month placebo-controlled portions of 12-month clinical studies (ie, baseline to Month 4), R
Solution demonstrated the following effica

- **Hair Counts.** ROGAINE was significant
than placebo in producing hair regrowth as
counts. Patients using ROGAINE had a me
baseline of 72 non-vellus hairs in the one i
cle compared with a mean increase of 39 n
patients using the placebo ($P < 0.0005$).
- **Investigator Evaluation.** Based on the in
uation, there was no statistically signific
terminal hair regrowth between treatme
percent (8%) of the patients using ROGAI
moderate to dense terminal hair regrowt
4% using the placebo. During the initial
treatment, however, very little regrowth
can be expected. Although most patients
strate cosmetically significant regrowth of
patients showed minimal terminal hair
ROGAINE compared with 16% of those
assessed by the investigator.
- **Patient Evaluation.** Based on the patient
26% using ROGAINE demonstrated moder
regrowth compared with 11% using the plac

Patients who continued on ROGAINE d
placebo-controlled portion of the studies (ie,
months of the 12-month clinical studies) cont
a regrowth response as evaluated by hair c
tor evaluation, and patient evaluation.

At the end of the eight month non-placebo-cc
of the 12-month clinical studies (ie, Months
lowing results were obtained.

- **Hair Count.** Patients using ROGAINE
crease of 112 non-vellus hairs in the same or
circle as compared to Month 4 ($P < 0.0005$).
- **Investigator Evaluation.** Based on the inv
uation, 39% of the patients achieved moder
minal hair by Month 12.
- **Patient Evaluation.** Based on the patie
48% felt they had achieved moderate to dens
at Month 12.

Trends in the data suggest that those patient
ger, who have been balding for a shorter pe
who have a smaller area of hair loss may resp
patients who are older, who have been bald
period of time, or who have a larger area o

CLINICAL TRIAL EXPERIENCE—FEM

In clinical trials in **females** (age range 18–45
were Caucasian) with Ludwig grade I and II d
rietal hair thinning, the main parameters o
non-vellus hair counts in a designated 1.0
frontoparietal areas of the scalp; investigat
hair regrowth; and patient evaluation of hair
demonstrate that 44% to 63% (investigat
from the international and US multicente
tively) of women with androgenetic alopeci
cernible growth of non-vellus hair when
ROGAINE for 32 weeks versus 29% to 39%
trol treated women.

Two 8-month placebo-controlled studies in fe
ticenter trial and an international multice
duced the following results:

- **Hair Counts.** ROGAINE was significantly
than placebo in producing hair regrowth as a
counts in both studies. Patients using ROGAI
increase from baseline of 22.7 and 33.2 non
the two trials, respectively, in the same 1.0
pared with a mean increase of 11.0 and 19.1 n
respectively, in patients using placebo (
$p = 0.0001$, respectively).
- **Investigator Evaluation.** Based on the inv
uation 63% (13% moderate and 50% mini
(12% moderate and 32% minimal), respecti
tients using ROGAINE in the two studies ac
growth at Week 32, compared with 39% (6%
33% minimal) and 29% (5% moderate and
respectively, of those using placebo ($p < 0.000$
respectively).
- **Patient Evaluation.** Based on the patients'
59% (19% moderate and 40% minimal) and 5
24% moderate, and 30% minimal), respecti
tients using ROGAINE reported hair regrow
compared with 40% (7% moderate and 33%
41% (12% moderate and 29% minimal), r
those using placebo ($p = 0.002$ and $p = 0.013$,

New hair growth was rated as follows:

Investigator Evaluation:

No visible new growth

Minimal: Definite growth but no substanti
thinning areas.

Moderate: New growth partially covering t
less dense than non-thinning areas (readily
Dense: Full covering of thinning areas; densi
lar to non-thinning areas

ment Evaluation:
visible new hair growth
minal: Barely discernible
erate: Readily discernible
ss

ICATIONS AND USAGE
GAINE Topical Solution is indicated for the treatment of
ogenetic alopecia, expressed in males as baldness of the
ex of the scalp and in females as diffuse hair loss or thin-
g of the frontoparietal areas. At least four months of
e daily applications of ROGAINE are generally required
ore evidence of hair growth can be expected.

NTRAINDICATIONS
GAINE Topical Solution is contraindicated in those pa-
ts with a history of hypersensitivity to any of the compo-
ts of the preparation.

RNINGS
ed for normal scalp
majority of clinical studies included only healthy pa-
ts with normal scalps and no cardiovascular disease.
ore starting a patient on ROGAINE, the physician should
rtain that the patient has a healthy, normal scalp. Local
tion or dermatitis may increase absorption and hence
ease the risk of side effects.
otential adverse effects
though extensive use of topical minoxidil has not revealed
idence that enough minoxidil is absorbed to have systemic
ects, greater absorption because of misuse or individual
sitivity or unusual sensitivity could lead, at least theoret-
ally, to a systemic effect, and physicians and patients need
be aware of this.
perience with oral minoxidil has shown the following ma-
cardiovascular effects (the package insert for
NTEN®, minoxidil tablets, should be reviewed for de-
ls):
id and water retention, generalized and local edema
ericardial effusion, pericarditis, tamponade
achycardia
creased frequency of angina or new onset of angina
ystemic effects were to occur, patients with underlying
rt disease, including coronary artery disease and conges-
heart failure, would be at particular risk. Minoxidil
ld also have additive effects with other therapy in pa-
ts being treated for hypertension.
ients being considered for ROGAINE Topical Solution
uld have a history and physical examination. Patients
uld be advised of the potential risk and a decision should
ade by the patient and physician that the benefits out-
gh the risks. Patients with a history of underlying heart
ase should be aware that adverse effects in them might
specially serious. Patients should be alerted to the possi-
ity of tachycardia and fluid retention and should watch
and be monitored for, increased heart rate and weight
n or other systemic effects.

CAUTIONS
neral Precautions
ients treated with ROGAINE Topical Solution should be
nitored one month after starting ROGAINE and at least
ry six months thereafter. If systemic effects should occur,
ntinue use of ROGAINE.
GAINE contains an alcohol base which will cause burn-
and irritation of the eye. In the event of accidental con-
with sensitive surfaces (eye, abraded skin, and mucous
mbranes), the area should be bathed with large amounts
ool tap water.
GAINE should not be used in conjunction with other topi-
agents including topical corticosteroids, retinoids, and
rolatum or agents that are known to enhance cutaneous
g absorption.
GAINE is for Topical Use Only. Each milliliter of
GAINE contains 20 mg minoxidil. Accidental ingestion of
solution could lead to possible adverse systemic effects
e OVERDOSAGE.)
s the case with other topically applied drugs, decreased
grity of the epidermal barrier caused by inflammation or
ease processes in the skin (eg, excoriations of the scalp,
p psoriasis, or severe sunburn) may increase percutane-
absorption of minoxidil.
rmation for the Patient
patient information leaflet has been prepared and is in-
ded with each package of ROGAINE. The text of the leaf-
is printed at the end of this insert.
g Interactions
ere are currently no known drug interactions associated
h the use of ROGAINE Topical Solution. Although it has
been clinically demonstrated, there exists the theoretical
ssibility of absorbed minoxidil potentiating orthostatic
potension in patients concurrently taking guanethidine.
rcinogenesis, Mutagenesis, and Impairment of Fertility
-year carcinogenicity studies of minoxidil have been
nducted by the dermal and oral (dietary) routes of adminis-
tion in mice and rats. There were no positive findings
h the oral (dietary) route of administration in rats.
In the two-year dermal study in mice, an increased incidence of mammary adenomas and adenocarcinomas in the females at all dose levels (8, 25 and 80 mg/kg/day) was attributed to increased prolactin activity. Hyperprolactinemia is a well-known mechanism in the enhancement of mouse mammary tumors, but has not been associated with mammary tumorigenesis in women. Additionally, topical minoxidil has not been shown to cause hyperprolactinemia in women on clinical trials. Absorption of minoxidil through rodent skin is greater than would be experienced by patients treated topically with minoxidil for hair loss. Dietary administration of minoxidil to mice for up to 2 years was associated with an increased incidence of malignant lymphomas in females at all dose levels (10, 25 and 63 mg/kg/day) and an increased incidence of hepatic nodules in males (63 mg/kg/day). There was no effect of dietary minoxidil on the incidence of malignant liver tumors.
In the two-year dermal study in rats there were significant increases in incidence of pheochromocytomas in males and females and preputial gland adenomas in males. Changes in incidence of neoplasms found to be increased in the dermal or oral carcinogenicity studies were typical of those expected in rodents treated with other hypotensive agents (adrenal pheochromocytomas in rats), treatment-related hormonal alterations (mammary carcinomas in female mice; preputial gland adenomas in male rats) or representative of normal variations within the range of historical incidence for rodent neoplasms (malignant lymphomas, liver nodules/adenomas in mice). Based on differences in absorption of minoxidil and mechanisms of tumorigenesis in these rodent species, none of these changes were considered to be relevant to the safety of patients treated topically with minoxidil for hair loss.
There was no evidence of epithelial hyperplasia or tumorigenesis at the sites of topical application of minoxidil in either species in the 2-year dermal carcinogenesis studies. No evidence of carcinogenicity was detected in rats or rabbits treated topically with minoxidil for one year. Topical minoxidil (2% and 5%) did not significantly ($p < 0.05$) reduce the latency period of UV light-initiated skin tumors in hairless mice, as compared to controls, in a 12-month photocarcinogenicity study.
Minoxidil was not mutagenic in the *Salmonella* (Ames) test, the DNA damage alkaline elution assay, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay, the rat bone marrow micronucleus assay, or the mouse bone marrow micronucleus assay. An equivocal result was recorded in an *in vitro* cytogenetic assay using Chinese hamster cells at long exposure times, but a similar assay using human lymphocytes was negative.
In a study in which male and female rats received one or five times the maximum recommended human oral antihypertensive dose of minoxidil (multiples based on a 50 kg patient) there was a dose-dependent reduction in conception rate.

Pregnancy
Pregnancy Category C. Adequate and well-controlled studies have not been conducted in pregnant women treated with ROGAINE Topical Solution nor in pregnant women treated with oral minoxidil for hypertension. Oral administration of minoxidil has been associated with evidence of increased fetal resorption in rabbits, but not rats, when administered at five times the maximum recommended oral antihypertensive human dose. There was no evidence of teratogenic effects of ORALLY administered minoxidil in rats or rabbits. Subcutaneous administration of minoxidil to pregnant rats at 80 mg/kg/day (approximately 2000 times the maximal systemic human exposure from daily topical administration) was maternally toxic but not teratogenic. Higher subcutaneous doses produced evidence of developmental toxicity. ROGAINE should not be administered to pregnant women.

Labor and Delivery
The effects on labor and delivery are unknown.

Nursing Mothers
There has been one report of minoxidil excretion in the breast milk of a woman treated with 5 mg oral minoxidil twice daily for hypertension. Because of the potential for adverse effects in nursing infants from minoxidil absorption, ROGAINE should not be administered to a nursing woman.

Pediatric Use
Safety and effectiveness in patients under 18 years of age have not been established.

Post-Menopausal Use
Efficacy in post-menopausal women has not been studied.

ADVERSE REACTIONS
ROGAINE Topical Solution has been used by 3,857 patients (347 females) enrolled in placebo-controlled trials. The rate of adverse events, grouped by body system, is shown in the following table. Except dermatologic events, which were more common in the minoxidil group, no individual reaction or body system grouping seemed to be increased in the minoxidil-treated group.
[See table at top of next page.]
Patients have been followed for up to 5 years and there has been no change in incidence or severity of reported reactions. Additional events reported in postmarketing clinical experience include: eczema, hypertrichosis (including facial hair growth in women), local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances including decreased visual acuity, exacerbation of hair loss, alopecia.

OVERDOSAGE
Increased systemic absorption of minoxidil may potentially occur if more frequent or larger doses of ROGAINE (than directed) are used or if ROGAINE is applied to large surface areas of the body or areas other than the scalp. There are no known cases of minoxidil overdosage resulting from topical administration of ROGAINE.
In a 14-day controlled clinical trial, 1 mL of 3% minoxidil solution was applied eight times daily (six times the recommended dose) to the scalp of 11 normal male volunteers and to the chest of 11 other volunteers. No significant systemic effects were observed in these subjects when compared with a similar number of placebo-treated subjects. All subjects in the study were monitored for vital sign, electrocardiographic, and echocardiographic changes.
In a reported case of accidental ingestion, a 3-year-old male swallowed 1 to 2 mL of a 3% concentration of topical minoxidil solution. After vomiting he was treated in an emergency room. The child was found to be alert and active with no obvious signs of distress. His temperature was 37° C, pulse 152 bpm, respiration 32, and systolic blood pressure 110 by palpation. Cardiovascular, chest, lungs, abdomen, head, skin, and neurological examinations were normal. Blood levels taken indicated a total minoxidil level (glucuronide and unchanged) of 320.6 ng/mL. The child was discharged without sequelae.
Because of the high concentration of minoxidil in ROGAINE Topical Solution, accidental ingestion has the potential of producing systemic effects related to the pharmacologic action of the drug (5 mL of ROGAINE Topical Solution contains 100 mg minoxidil, the maximum adult dose for oral minoxidil administration when used to treat hypertension). Signs and symptoms of minoxidil overdosage would most likely be cardiovascular effects associated with fluid retention and tachycardia. Fluid retention can be managed with appropriate diuretic therapy. Clinically significant tachycardia can be controlled by administration of a beta-adrenergic blocking agent. If encountered, hypotension should be treated by intravenous administration of normal saline. Sympathomimetic drugs, such as norepinephrine and epinephrine, should be avoided because of their excessive cardiac stimulating activity.
Oral LD_{50} in rats has ranged from 1321 to 3492 mg/kg; in mice 2457 to 2648 mg/kg. Minoxidil and its metabolites are hemodialyzable.

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry prior to topical application of ROGAINE Topical Solution. A dose of 1 mL ROGAINE Topical Solution should be applied to the total affected areas of the scalp twice daily. The total daily dosage should not exceed 2 mL. If finger tips are used to facilitate drug application, hands should be washed afterwards. Twice daily application for four months or longer may be required before evidence of hair regrowth is observed. Onset and degree of hair regrowth may be variable among patients. If hair regrowth is realized, twice daily applications of ROGAINE appear necessary for additional or continued hair regrowth. Some anecdotal patient reports indicate that regrown hair and the balding process return to their untreated state three to four months following cessation of the drug.

HOW SUPPLIED
ROGAINE Topical Solution is a clear, colorless, to light yellow solution containing 20 mg minoxidil per mL in a 60 mL bottle and is available as:

one—60 mL bottle with dropper	NDC 0009-3367-05
three—60 mL bottles with dropper	NDC 0009-3367-19

Store at controlled room temperature: 15° to 30° C (59° to 86° F).

CAUTION
Federal law prohibits dispensing without a prescription.

IMPORTANT INFORMATION ABOUT—
ROGAINE® Topical Solution (minoxidil 2%)
Your doctor has prescribed ROGAINE Topical Solution for you to use as a hair regrowth stimulant to treat alopecia androgenetica (hair loss). ROGAINE is a prescription medication and therefore should be used only as directed by your doctor.
Please read this booklet thoroughly. It will help you to understand ROGAINE Topical Solution and what to expect from its use. If you have any questions after reading this

Continued on next page

Information on these Upjohn products is based on labeling in effect June 1, 1995. Further information concerning these and other Upjohn products may be obtained by direct inquiry to Medical Information, The Upjohn Company, Kalamazoo, Michigan 49001.

Upjohn—Cont.

Medical Event Percent Occurrence By Body System In The Placebo-Control Clinical Trials Involving Minoxidil Topical Solution —All Patients Enrolled

BODY SYSTEM	Minoxidil Soln N=3857 (4–8 months) # PATS.	% OCC.	Placebo N=2717 (4–8 months) # PATS.	% OCC.
DERMATOLOGICAL (irritant dermatitis, allergic contact dermatitis)	284	7.36	147	5.41
RESPIRATORY (bronchitis, upper respiratory infection, sinusitis)	276	7.16	233	8.58
GASTROINTESTINAL (diarrhea, nausea, vomiting)	167	4.33	178	6.55
NEUROLOGY (headache, dizziness, faintness, light-headedness)	132	3.42	94	3.46
MUSCULOSKELETAL (fractures, back pain, tendinitis, aches and pains)	100	2.59	60	2.21
CARDIOVASCULAR (edema, chest pain, blood pressure increases/decreases, palpitations, pulse rate increases/decreases)	59	1.53	42	1.55
ALLERGY (non-specific allergic reactions, hives, allergic rhinitis, facial swelling, and sensitivity)	49	1.27	26	0.96
METABOLIC-NUTRITIONAL (edema, weight gain)	48	1.24	35	1.29
SPECIAL SENSES (conjunctivitis, ear infection, vertigo)	45	1.17	33	1.21
GENITAL TRACT (prostatitis, epididymitis, pregnancy, vaginitis, vulvitis, vaginal discharge and itching)	35	0.91	22	0.81
URINARY TRACT (urinary tract infections, renal calculi, urethritis)	36	0.93	31	1.14
ENDOCRINE (menstrual changes, breast symptoms)	18	0.47	14	0.52
PSYCHIATRIC (anxiety, depression, fatigue)	14	0.36	26	0.96
HEMATOLOGY (lymphadenopathy, thrombocytopenia, anemia)	12	0.31	15	0.55

booklet, or anytime during treatment with ROGAINE, you should consult your doctor or ask your pharmacist.

What is ROGAINE?

ROGAINE Topical Solution, discovered and made by The Upjohn Company, is a standardized topical (for use only on the skin) prescription medication proved effective for the treatment of alopecia androgenetica (hair loss).

ROGAINE is a topical solution of minoxidil. Minoxidil in tablet form has been used since 1980 to lower blood pressure. The use of ***minoxidil tablets*** is limited to treatment of patients with severe high blood pressure. When a high enough dosage in tablet form is used to lower blood pressure, certain effects that merit your attention may occur. These effects appear to be dose related. (See [What are the potential side effects on the heart and circulation when using ROGAINE?])

Persons who use ROGAINE Topical Solution have a low level of absorption of minoxidil, much lower than that of persons being treated with ***minoxidil tablets*** for high blood pressure. Therefore, the likelihood that a person using ROGAINE Topical Solution will develop the effects associated with ***minoxidil tablets*** is very small. In fact, none of these effects has been directly attributed to ROGAINE in clinical studies.

Exactly how ROGAINE works to stimulate hair growth in some people is not known. Upjohn scientists are doing research in this area.

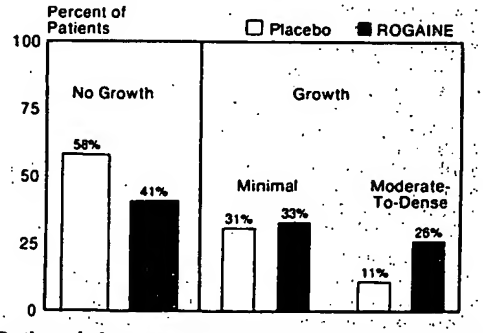
How effective is ROGAINE?

Males

Clinical studies with ROGAINE were conducted by physicians in 27 U.S. medical centers involving over 2,300 patients with male pattern baldness involving the top (vertex) of the head. At the end of four months, hair counts showed that on average, the patients using ROGAINE Topical Solution had significantly more hair growth than those who used placebo (a similar solution without the active medication).

Based on the patients' self-evaluation at the end of four months, 59% of the patients using ROGAINE had minimal to dense hair growth compared with 42% of those using placebo. Below is a bar chart illustrating patients' self evaluation of hair growth.

Male Results
Patient Self Evaluation of Hair Regrowth at 4 Months
Combined Results of 27 U.S. Medical Centers



By the end of one year, 48% of the people who continued in the study using ROGAINE rated their hair growth as moderate or better.

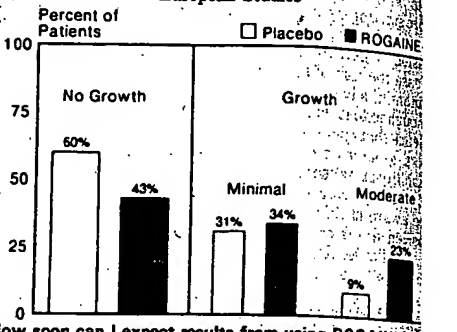
Females

Clinical studies with ROGAINE were conducted by physicians in eleven U.S. and ten European medical centers involving over 600 female patients with hair loss. Based on actual hair counts, the women using ROGAINE had significantly more hair regrowth at the end of eight months than those who used placebo (a similar solution without the active medication).

Based on the patients' self evaluation, 59% of the U.S. patients using ROGAINE reported hair regrowth at Week compared with 40% of those using placebo. Of the 59% porting hair regrowth, 19% reported moderate and reported minimal hair growth. In the European study, percentage of patients reporting hair regrowth at Week was 55% among the ROGAINE users compared with among the placebo patients. Of the 55% reporting hair growth, 1% reported dense, 24% reported moderate 30% reported minimal hair growth.

In the combined results of the U.S. and European studies 57% of the women using ROGAINE evaluated their regrowth as minimal or moderate after 32 weeks compared to 40% of those using placebo. Below is a bar chart illustrating patients' self evaluation of hair regrowth.

Female Results
Patient Self Evaluation of Hair Regrowth at 32 Weeks
Combined Results of U.S. & European Studies



How soon can I expect results from using ROGAINE?

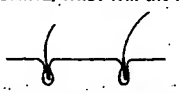
Studies have shown that the response to treatment w ROGAINE may vary widely. If you respond to treatment usually will take four months or longer before there is dence of hair growth.

Hair growth is cyclical in nature. The hair growth phase scalp follicle lasts two to six years. Then the hair follicle gins a two to six month resting phase. As new hair grow begins, old hairs are released from the scalp resulting shedding.

Upon initiation of ROGAINE therapy some follicles may shifted from the resting phase into the growth phase resu ing in a temporary increase in shedding. This increase shedding generally occurs two to six weeks after beginn treatment and subsides within a few weeks. If increas shedding persists, other causes of hair loss will need to ruled out by your physician.

Remember, successful hair growth can only be evaluat after continuous twice a day treatment for four months longer.

If I respond to ROGAINE, what will the hair look like?



If you have very little hair and respond to treatment, yo first hair growth may be soft, downy, colorless hair that barely visible. After further treatment the new hair shou be the same color and thickness as the other hair on yo scalp. If you start with substantial hair, the new hair shou be of the same color and thickness as the rest of your hai

How long do I need to use ROGAINE?

ROGAINE is a treatment, not a cure. If you respond to trea ment, you will need to continue using ROGAINE to mainta or increase hair growth. If you do not begin to show a sponse to treatment with ROGAINE after a reasonable p riod of time (at least four months or more), your doctor m advise you to discontinue using ROGAINE.

What happens if I stop using ROGAINE? Will I keep the ne hair?

If you stop using ROGAINE, you will probably shed the ne hair within a few months after stopping treatment.

What is the dosage of ROGAINE?

You should apply a 1 mL dose of ROGAINE two times a da once in the morning and once at night. Each bottle shou last about 26–30 days. A bottle of ROGAINE ¾ full. This fill level is intentional to allow for product di placement when the dropper is inserted in the bottle. T dropper in each package of ROGAINE is designed to appl the correct amount of ROGAINE with each applicatio *Please refer to the Instructions for Use.*

Can I apply ROGAINE and wash it out an hour later?

No. After applying ROGAINE it must remain on the scal for at least 4 hours so that the medication may be absorbe into the scalp. If you prefer, you may wash your hair befo applying ROGAINE but the scalp and hair must dry befo the application.

…times I see a residue on my hair. Is this harmful?
…me people. ROGAINE will dry in the hair and leave a …residue. This harmless residue was noted by a small …ber of patients during the clincial trials for ROGAINE. …effectiveness of the product is not altered by the …ence of the residue.

…If I miss a dose or forget to use ROGAINE?
…miss one or two daily applications of ROGAINE, you …ld restart your twice-daily application and return to …ginal schedule. You should not attempt to make up for …ed applications.

…I use ROGAINE more than twice a day? Will it work …re?
…tudies by The Upjohn Company have been carefully …cted to determine the correct amount of ROGAINE to …o obtain the most satisfactory results. More frequent …ations or use of larger doses (more than 1 mL twice a …ay) have not been shown to speed up the process of hair …th and may increase the possibility of side effects.

…are the most common side effects reported in clinical …s with ROGAINE?
…s of patients using ROGAINE have shown that the …common adverse effects directly attributable to …INE Topical Solution were itching and other skin irri… of the treated area of the scalp.
…side effects, including light-headedness, dizziness, and …hes were reported by patients using ROGAINE or …o (a similar solution without the active medication). …equency of these side effects was similar in the …INE and placebo groups. For further information …side effects please ask your doctor.

…OGAINE produce unwanted hair growth?
…hair growth has been reported by some users of …NE, particularly females. While the cause is un…it may be related to the continuous inadvertent expo…the face to the medication. Another possible explana…that some hair follicles, mostly, but not exclusively on …may be extremely sensitive to very low levels of the …ion absorbed from the scalp.
…imize the likelihood of hair growth on the forehead or …wash your hand after ROGAINE application to the …d be as careful as possible to avoid transferring the …on from your scalp to other parts of the body.

…e the potential side effects on the heart and circula…n using ROGAINE?
…o serious side effects have not been attributed to …E in clinical studies, there is a possibility that they …ur because the active ingredient in ROGAINE Topi…ion is the same as in *minoxidil tablets*.
…l tablets are used to treat high blood pressure.
…l tablets lower blood pressure by relaxing the arter…ect called vasodilation. Vasodilation leads to reten…uid and increased heart rate. The following effects …urred in some patients taking *minoxidil tablets* for …d pressure:
…ed heart rate. Some patients have reported that …ing heart rate increased by more than 20 beats per …

…weight gain of more than 5 pounds or swelling …the face, hands, ankles, or stomach area.
…ty in breathing, especially when lying down, a re…increase in body fluids or fluid around the heart.
…ing of, or new onset of, angina pectoris.
…AINE Topical Solution is used on normal skin, …minoxidil is absorbed and these effects are not …f, however, you experience any of the above, dis…se of ROGAINE and consult your doctor. Presum…effects would be most likely if greater absorption …g, because ROGAINE was used on damaged or …kin or in greater than recommended amounts. …studies, minoxidil, in doses higher than would be …om topical use in people, has caused important …ture damage. This kind of damage has not been …nans given *minoxidil tablets* for high blood pres…ctive doses.

…rs may increase the risk of serious side effects …INE?
…with known or suspected underlying coronary …se, or the presence of or predisposition to heart …ld be at particular risk if systemic effects (that is, …art rate or fluid retention) of minoxidil were to …cians, and patients with these kinds of underly…, should be conscious of the potential risk of …they choose to use ROGAINE.
…orption of minoxidil may be increased and the …ffects may become greater, ROGAINE should be …to the scalp and should not be used on other …ody. You should not use ROGAINE if your scalp …tated or is sunburned, and you should not use it …her topical treatment medication on your scalp.

…with high blood pressure use ROGAINE?
…with hypertension, including those under treat…ntihypertensive agents, can use ROGAINE but …nitored closely by their doctor. Patients taking …for high blood pressure should not use …

Will ROGAINE change my menstrual cycle?
No. Carefully conducted studies have shown that the use of ROGAINE will not increase the length of the menstrual cycle (interval between periods) or change the amount of flow or duration of the menstrual period. However, if your menstrual period does not occur at the expected time, you should discontinue the use of ROGAINE and consult your doctor as soon as possible.

Should I continue to use ROGAINE if I desire to become pregnant?
If you plan to become pregnant, you should discontinue using ROGAINE at least one month before you discontinue your birth control. Adequate and well-controlled studies have not been conducted in pregnant women treated with ROGAINE or in pregnant women taking oral minoxidil for the treatment of high blood pressure.

Can nursing mothers use ROGAINE?
No. We do not have any data from clinical trials or voluntary reports on minoxidil being reported in the breast milk following use of ROGAINE. It should be noted, however, that there has been one report of minoxidil excretion in the breast milk of a woman treated with 5 mg oral minoxidil twice daily for hypertension. Consequently, ROGAINE should not be administered to a nursing woman.

INSTRUCTIONS FOR USE
WARNING: Do not use product if the tamper-evident ring on the child-resistant closure has been broken. Like all medications, ROGAINE should be kept out of the reach of children. ROGAINE Topical Solution contains alcohol, which could cause burning or irritation of the eyes, mucous membranes, or sensitive skin areas. If ROGAINE accidentally gets into these areas, bathe the area with large amounts of cool tap water. Contact your doctor if irritation persists. If you swallow ROGAINE contact your doctor. If you have any questions after reading this, please ask your doctor or pharmacist.
One mL (or 1 dose) of ROGAINE should be applied to the affected area of the scalp twice daily. The hair and scalp should be dry before application of ROGAINE. ROGAINE must be applied directly to the scalp. Applying ROGAINE to the hair will not help it grow.
Each prescription of ROGAINE comes with a metered dropper for use in applying the ROGAINE solution. The dropper is designed to deliver a measured amount (1 mL, or 1 dose) of solution when used as directed. It is normal for a small amount of product to remain in the dropper tip. One (1) mL of ROGAINE has been used in clinical studies and determined to be the proper amount for the treatment of androgenetic alopecia (hair loss). Twice-daily application for four months or longer may be required before hair regrowth may be observed.

APPLICATION
1. Remove the large outer cap and the small inner child-resistant, tamper-evident cap. The child-resistant cap can be removed with a firm downward counter-clockwise motion. Both caps should be saved for reuse.
2. Squeeze the rubber bulb on the end of the dropper and insert into the bottle. Release the bulb, allowing the dropper to fill to the 1 mL line. If the level of the solution is above the 1 mL line, squeeze the extra solution back into the bottle.
3. Place the tip of the dropper against the scalp in the area to be treated. Gently squeeze the dropper to gradually release the solution as you move the tip across the area to be treated. To keep the solution from dripping off the scalp, only apply a small amount in one place at one time. If you use your fingertips to rub the solution into the scalp, be sure to wash your hands after applying.
4. To avoid leakage when traveling, reapply the child-resistant cap to the bottle and tighten securely. When securely tightened, the cap will no longer turn in a clockwise direction. Reapply the large outer cap. In the case of an accidental spill, wipe the surface immediately to avoid the possibility of staining.

Revised September 1994 813 264 014
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Shown in Product Identification Guide, page 338

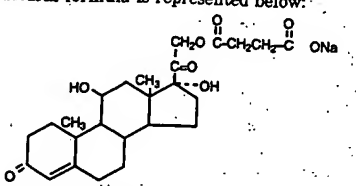
SOLU-CORTEF®

brand of hydrocortisone sodium succinate sterile powder (hydrocortisone sodium succinate for injection, USP) For Intravenous or Intramuscular Administration

℞

DESCRIPTION

SOLU-CORTEF Sterile Powder contains hydrocortisone sodium succinate as the active ingredient. Hydrocortisone sodium succinate is a white or nearly white, odorless, hygroscopic amorphous solid. It is very soluble in water and in alcohol, very slightly soluble in acetone and insoluble in chloroform. The chemical name is pregn-4-ene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-, monosodium salt, (11β)- and its molecular weight is 484.52.
The structural formula is represented below:



Hydrocortisone sodium succinate is an anti-inflammatory adrenocortical steroid. This highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly.
SOLU-CORTEF Sterile Powder is available in several packages for intravenous or intramuscular administration.
100 mg Plain—Vials containing hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone, also 0.8 mg monobasic sodium phosphate anhydrous, 8.73 mg dibasic sodium phosphate dried.
[See table on bottom of next page.]
When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8.

ACTIONS

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.
Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.
Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. Thus, if constantly high blood levels are required, injections should be made every 4 to 6 hours. This preparation is also rapidly absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after intravenous injection.

INDICATIONS

When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the condition, SOLU-CORTEF Sterile Powder is indicated for intravenous or intramuscular use in the following conditions:

1. Endocrine Disorders
Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance)
Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)
Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful
Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected
Congenital adrenal hyperplasia
Hypercalcemia associated with cancer
Nonsuppurative thyroiditis

2. Rheumatic Disorders
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
Post-traumatic osteoarthritis
Synovitis of osteoarthritis
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)

Continued on next page

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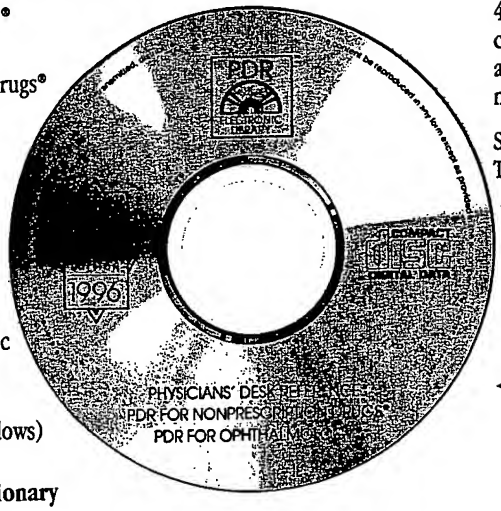

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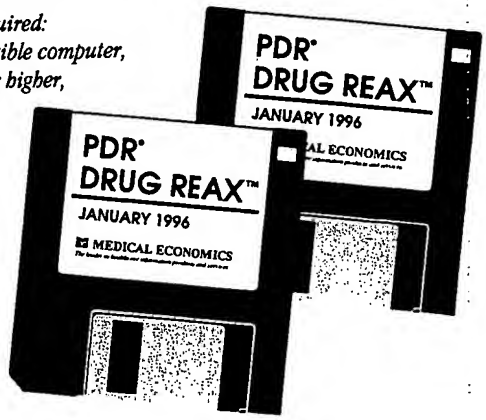

EVIDENCE 3

3. Sasson et al., "Status of Medical Treatment for Androgenic Alopecia" International J. Dermatology, 32(10): 701-706 (1993).

REVIEW

STATUS OF MEDICAL TREATMENT FOR ANDROGENETIC ALOPECIA

MARVIN SASSON, B.A.,

JEROME L. SHUPACK, M.D., AND MATTHEW J. STILLER, M.D.

The search for agents to promote hair growth has a long and sometimes jaded history. Only in the last 15 years has the medical community seriously investigated this therapeutic area. This paper will review the story of minoxidil and update the reader on newer clinical trials.

Androgenetic alopecia (AGA) occurs in both men and women. The pattern of hair loss varies by individual and gender, but in men it usually begins with a receding hairline with further loss at the vertex. As hair loss continues the areas of baldness merge leaving only a ring of hair around the scalp (Fig. 1). In women the pattern is slightly different sparing the anterior hairline and affecting predominantly the crown (Fig. 2).

PATHOGENESIS

The pathogenesis of AGA probably involves a genetic component as well as susceptibility to androgens. However, the exact determinants of scalp hair loss and pattern of loss are not fully understood. Hamilton first suggested causal roles for testosterone and heredity in AGA.[1] He noted that men castrated before puberty had no regression of the frontal hairline and balding men castrated as adults developed no further frontal recession. When castrated men with a family history of AGA were given testosterone, their hair line receded. In contrast, men with no familial baldness retained their hair when treated with testosterone. Genetically AGA may be either autosomal dominant with variable penetrance[2] or polygenic.[3]

In 1965 topical testosterone was first reported to be trichogenic.[4] This was soon disproved[5] and interest in hair research waned. Ten years ago initial reports on the efficacy of minoxidil in male-pattern baldness renewed interest in medical treatment of AGA (Table 1).

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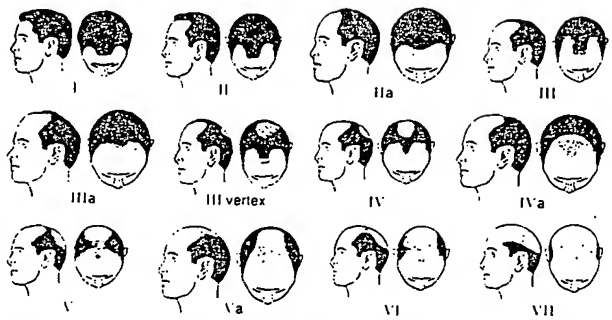

Figure 1. The Hamilton-Norwood classification for androgenetic alopecia in men.

MINOXIDIL

The antihypertensive drug minoxidil is the only approved treatment for AGA. This potent vasodilator acts directly on peripheral arterioles decreasing blood pressure with resultant tachycardia.[6] Hypertrichosis occurred in most patients taking minoxidil chronically for hypertension.[7-9] Zappacosta[10] and Siedman et al.[11] reported reversal of AGA in patients treated with oral minoxidil. In 1981 Weiss et al.[12] reported hair growth in two patients with alopecia areata treated with topical minoxidil.

The mechanism of minoxidil in promoting hair growth is incompletely understood. Its effect on scalp blood flow has been proposed. Cutaneous blood flow is decreased in AGA.[13] Minoxidil increases cutaneous blood flow to the scalp[14] possibly promoting hair growth by this mechanism. Other antihypertensive agents, including viprostol and diazoxide, increase cutaneous blood flow but are ineffective in promoting hair growth.

Figure 2. The Ludwig classification for androgenetic alopecia in women.

Table 1. Drugs Evaluated for the Treatment of Androgenetic Alopecia

Agent	*Postulated Mechanism of Action*	*Study Type*	*Route of Administration*	*Efficacy*	*Availability*
Minoxidil	Vasodilator; direct effect on the dermal papilla or hair matrix cells	Multicenter Double-blind Placebo-controlled	Topical	Yes	Available FDA approved
Minoxidil + Tretinoin	Vasodilator; enhanced absorption	Single center Double-blind Placebo-controlled	Topical	Yes	Available Not FDA approved
Viprostol	Vasodilator	Multicenter Double-blind Placebo-controlled	Topical	No	Not available
Diazoxide	Vasodilator	Pilot study	Topical	Uncertain	Not available
Omexin	Angiogenesis	Multicenter Double-blind Placebo-controlled	Topical	Uncertain	Not available
Cyclosporine	Uncertain	Pilot Study	Oral/Topical	Yes	Available Not FDA approved
Spironolactone	Antiandrogenic	Pilot Study	Oral	Yes	Available Not FDA approved
Cimetidine	Antiandrogenic	Pilot Study	Oral	Yes	Available Not FDA approved
Inocoterone acetate	Antiandrogenic	Multicenter Double-blind Placebo-controlled	Topical	Uncertain	Not available

Headington[15] proposed a direct effect of minoxidil on the dermal papilla or on follicular hair matrix cells. Scalp biopsies of balding men treated with topical minoxidil showed reversal of the follicular miniaturization seen in AGA. Incubation of mouse vibrissae follicles with minoxidil resulted in increased cysteine incorporation and longer hairs.[16] Minoxidil has also been shown to increase epithelial cell proliferation in culture.[17] These data support claims that minoxidil directly affects cells in the dermal papilla or follicular matrix.

The stumptailed macaque is a useful animal model for studying AGA. [18] Balding similar to that in humans beginning shortly after puberty occurs in nearly all macaques including females. Uno et al.[19–21] demonstrated the efficacy of topical minoxidil in these primates. All macaques had increased hair regrowth on the frontal scalp, although this was more prominent in younger monkeys and in those with less severe balding. Topical minoxidil activated resting follicles in the balding scalp inducing follicular enlargement and preventing progression of balding. When treatment was discontinued, all beneficial effects were reversed, and balding progressed.

Early use of topical minoxidil in humans involved extemporaneously formulated preparations.[22,23] Pilot studies yielded inconclusive results.[24–36] In 1983–1984 Upjohn sponsored a 2,326 subject, 12-month, double-blind, placebo-controlled study at 27 centers.[27–34] Men 18–50 years-old with vertex balding received either 2% or 3% minoxidil for 12 months or placebo solutions. Subjects receiving placebo crossed-over to 3% minoxidil after 4 months. Vellus and nonvellus hairs in a 1-inch circular target area in the center of each subject's balding vertex were clipped monthly and counted using a magnifying lens (Table 2). After 4 months patients applying 2% or 3% minoxidil had greater growth of nonvellus hairs than those receiving placebo. Mean nonvellus counts were 59% greater than baseline after 4 months, with an additional 58% increase after 1 year.[35] Patients applying placebo solution had significantly smaller increases in hair counts. Subjective evaluation by these investigators showed that 26% of minoxidil recipients had minimal, 7% moderate, and 0.7% dense regrowth at 4 months. At 12 months 36% showed minimal, 31% moderate, and 8% dense regrowth. The best response was seen in patients less than 40-years-old with balding vertices less than 10 cm in diameter. Long-term studies for up to 2 years 9 months showed maintenance of regrowth in many patients.[30,33] In a 5-year follow-up of patients treated with topical minoxidil, nonvellus hair counts above baseline were still evident.[36]

Shupack et al.[28] investigated the dose-response to various concentrations of topical minoxidil. After 6 months patients using 0.1%, 1%, and 2% solutions showed a significantly greater mean increase of nonvellus hair growth than those using 0.01% minoxidil or placebo. There was a dose-response correlation for the increase of nonvellus hairs in the 0.1%, 1%, and 2% minoxidil treatment groups. Only patients treated with the 1% and 2% solutions of minoxidil had cosmetically acceptable hair growth.

Table 2. Methods for Evaluating Hair Loss and/or Regrowth

Increasing Accuracy ↓
Subjective assessment by patient of amount of shedding and/or regrowth.
Subjective assessment by investigator of regrowth.
Manual hair counting macroscopically *in vivo* in designated area on balding vertex marked by tattoo or in relation to facial anatomy.
Hair counting by macrophotography in designated area.
High-resolution ultrasound using 35–50 MHz transducer.*
Hair counting in designated area using laser optic scanner similar to supermarket bar-code reader or device used in bakeries to count sesame seeds on buns.*

*Under investigation by one of the authors (JLS).

Topical minoxidil is safe and lacks the systemic effects of the oral formulation. In the multicenter study there were no changes in mean blood pressure, pulse rate, or weight. Common cutaneous adverse reactions included erythema, scaling, pruritus, and dermatitis.[37] No deaths have been attributed to topical use of minoxidil.[38]

OTHER FORMULATIONS

Recent minoxidil studies have focused on developing improved formulations or combining minoxidil with other trichogenic drugs. Bazzano et al.[39] reported that topical tretinion alone or in combination with 0.5% minoxidil stimulated hair growth. Fifty-six patients were assigned to four treatment groups: twelve patients received 0.025% topical tretinion solution, 36 a combination of 0.025% tretinion and 0.5% minoxidil, three received 0.5% minoxidil, and five patients the vehicle containing 95% alcohol, 5% propylene glycol, and 1 mg butylated hydroxytoluene per 100 mL. Subjects applied 1 mL of solution to the affected area twice a day. Patients receiving either placebo or topical minoxidil alone had no response. Of the 12, 2 (16%) receiving tretinoin alone had a good response (46–1,400% increase in hair counts), while 5 of 12 (42%) had a moderate response (21–45% increase). Sixty-six percent of those receiving tretinoin combined with minoxidil had a moderate or good response.

Bazzano et al.[39] suggested that tretinoin may promote epithelial and vascular proliferation. Alternatively, tretinoin may act to increase the percutaneous absorption of minoxidil. Ferry et al.[40] studied the influence of tretinoin on the absorption of minoxidil. Patients received either a topical 2% minoxidil solution, 2% minoxidil combined with 0.05% tretinoin cream, or 2% minoxidil in a cream base. Cotreatment with tretinoin resulted in an almost threefold increase in minoxidil absorption, compared with a 1.3-fold increase with the cream vehicle. Transdermal water loss, a sensitive indicator of stratum corneum function,[41–43] was also measured and found to be 1.7 times greater in the tretinoin-treated group than the other two groups. Skin biopsies revealed no alteration in epidermal or stratum corneum thickness. These results suggest that increased absorption of minoxidil when combined with tretinoin is due to alteration of the barrier function of the stratum corneum. Studies are now underway to evaluate minoxidil in specialized solvent systems designed to enhance percutaneous absorption (Table 3).

The minoxidil experience has promoted studies of other antihypertensive agents for AGA. Hirsutism is a common side effect of systemic therapy with the hypotensive and hyperglycemic drug diazoxide. Roenigk[44] reported on a pilot study involving 60 patients testing 3% topical diazoxide. Twenty-five percent of subjects had some terminal hair growth. The complete details of this study have not been published. Olsen and DeLong[45] evaluated transdermal viprostol in the treatment of AGA in a double-blind, placebo-controlled clinical trial involving 57 men. Viprostol, a synthetic prostaglandin E_2 analog, is an effective antihypertensive drug. Hair counts in a 1-inch circle at the balding vertex assessed macrophotographically revealed decreased hair counts in viprostol-treated subjects. Both minoxidil and viprostol cause cutaneous vasodilation, so it is likely that minoxidil promotes hair growth through means other than vasodilatation.

The concepts that increased blood flow may be of benefit in AGA stimulated clinical trials to evaluate angiogenic factors. In the late 1980s an angiogenic extract of pig omentum, Omexin, was evaluated in men with Hamilton III-vertex, IV, and V AGA in a double-blind, placebo-controlled clinical trial at New York University Medical Center. This clinical trial was discontinued and the results have never been published.[46]

Table 3. Drugs Currently Under Investigation for Androgenetic Alopecia

Agent	*Manufacturer*	*Postulated Mechanism of Action*	*Study Type*	*Route of Administration*	*Safety*
Minoxidil in optimized vehicle	Upjohn	Vasodilator; enhanced absorption	Multicenter Double-blind Placebo-controlled	Topical	Under investigation
Finasteride	Merck	5α-reductase inhibitor	Multicenter Double-blind Placebo-controlled	Oral	Safe, based on use in benign prostatic hypertrophy

A side effect of the immunosuppressive drug cyclosporine is hypertrichosis.[47,48] Picascia and Roenigk[49] reported that all six psoriatic patients treated with systemic cyclosporine developed either hypertrichosis or thicker scalp hair. Systemically cyclosporine has potentially severe side effects especially nephrotoxicity and hypertension, but its topical use is presently under investigation. Roenigk[44] reported that 11 patients with AGA treated with 1% or 2% topical cyclosporine had a slight, cosmetically insignificant increase in hair growth after 4 months. More recently 13 patients were enrolled in a 12-month, double-blind, placebo-controlled study to determine the effectiveness of topical 5% cyclosporine.[50] Two of eight cyclosporine-treated subjects completing this clinical trial were considered treatment successes defined as a 50% increase in hair counts at 4 months and a 100% increase after 12 months.

The requirement of androgens for the development of male pattern baldness has spurred trials of oral and topical antiandrogens with various degrees of success. One such agent, spironolactone (SL), an aldosterone antagonist, has been used to treat hypertension, hyperaldosteronism, and congestive heart failure.[51] Antiandrogenic effects of SL, including decreased libido and gynecomastia, preclude its use in men. Spironolactone does not decrease levels of serum testosterone,[52] but it does compete with DHT for cytosolic receptors.[53,54] It has been used to treat acne,[55] hirsutism,[56] and AGA. Although there are few reports of the use of SL for AGA, some subjective improvement has been noted with doses of 50–200 mg/day.[57] Topically applied spironolactone has not yet been tested.

Cimetidine, a histamine H_2-receptor antagonist, used to treat peptic ulcers and reflux esophagitis, has antiandrogenic side effects in men including gynecomastia, impotence, and loss of libido. In one study of ten women treated with 300 mg orally five times a day, seven reportedly had good to excellent regrowth of hair.[58]

Inocoterone acetate (IA)[59,60] is an investigational compound with antiandrogenic activity when given subcutaneously or orally. The drug is active topically without any systemic antiandrogenic effect. This agent was tested in a double-blind, placebo-controlled, multicenter study on 76 men with AGA. However, these results have not been published.

Growth of hair in the pubic and axillary areas is testosterone-dependent, unlike scalp hair growth, which is affected by the conversion of testosterone to the potent metabolite dihydrotestosterone (DHT) by the enzyme 5α-reductase. Male subjects with an inherited deficiency of this enzyme are born with ambiguous genitalia but have otherwise normal growth and development. These patients virilize substantially at puberty but have only scant facial hair, no acne, a small prostate, and do not suffer from AGA.[61] Balding skin contains increased amounts of 5α-reduced testosterone metabolites including DHT and has higher 5α-reductase activity than nonbalding skin.[62,63] Inhibition of this enzyme may interfere with the process of balding. This was recently demonstrated in the stumptailed macaque, where N,N-diethyl-4-methyl-3-oxo-4-aza-5α-androstane-17β-carboxamide(4-MA), a 5α-reductase inhibitor and weak antiandrogen prevented the development of baldness.[64]

Finasteride, a systemic pure 5α-reductase inhibitor,[65,66] is currently under investigation for the treatment of male pattern baldness. Finasteride in combination with topical minoxidil has increased hair regrowth in the stumptailed macaque when compared to either drug alone.[67] The results of human trials are not yet available.

The search for a treatment for AGA has not been limited to topical and systemic medications. Mechanical devices have also been investigated (Table 4). The application of pulsed electrical stimulation (PES) proximal to the scalp (electrichogenesis), has been suggested as a method of inducing hair regrowth. Exogenous electrical signals have been shown to be beneficial in stimulating tissue repair in animal models[68] and humans.[69] In two pilot studies 84% of 25 patients and 70% of 40 patients experienced some hair regrowth after 60 days of treatment with a pulsed electrical field device.[70] Maddin et al.[71] enrolled 73 men with Hamilton III or IV AGA in a controlled study using this modality. The procedure involved weekly and twice weekly 12-minute treatments during which the patient's head was placed under a PES-device resembling a salon-type hair dryer. The device produced approximately 4,000 V/m, well below the estimated dangerous level of 3×10^8 V/m.[72] Fifty-six subjects completed the study, 30 in the PES-treated group and 26 controls. After 36 weeks PES-treated patients had a 66.1% increase in hair count, compared with a 25.6% increase in the control group. Most impressively, 96.7% of treated subjects exhibited

Table 4. Devices for Treating Androgenetic Alopecia

Device	*Manufacturer*	*Postulated Mechanism of Action*	*Study Type*	*Availability*	*Safety*
Pulsed electrical stimulation	Current Technology Corporation	Induces cell membrane depolarization leading to influx of calcium ions and transcription and translation	Multicenter Double-blind Placebo-controlled	Experimental	Safe No side effects
Scalp tension relaxer	Not in commercial development	Increased scalp blood flow as measured by Doppler flowmetry	Pilot study	Experiment	Safe No side effects

either regrowth or no further hair loss. The procedure is painless and free of side-effects. Results of a multicenter study in progress at New York University Medical Center and other sites in the U.S. and Canada have not been published.[73]

Japanese investigators postulated that increased scalp tension was a possible cause of AGA. They evaluated a device termed a scalp-tension-relaxer in the treatment of AGA.[74] The tourniquet-like apparatus fits around the forehead and occiput, while inflatable wedge-shaped rubber bags attached to the inside of the device are filled with air to push up the scalp and relieve tension. Subjects in this study used the apparatus two hours daily for up to 12 months. Sixteen of 40 patients (40%) had good to excellent improvement of AGA, defined as increased terminal hair over the periphery or entire area of alopecia. Judgements of efficacy were based on subjective gross evaluations of photographs. No hair counts were obtained. Only subjects with Hamilton type III-vertex and IV alopecia responded. Cutaneous blood flow to the scalp determined by laser Doppler flowmetry increased after application of the device, leading the authors to suggest this was the probable mechanism for hair regrowth.

CONCLUSION

We have reviewed research in medical treatment of AGA. This is an area in which exciting new developments can be anticipated in the coming years.

DRUG NAMES

cimetidine: Tagamet Tablets
cyclosporine: Sandimmune Soft Gelatin Capsules
diazoxide: Hyperstat I.V. Injection, Proglycem Capsules
minoxidil: Loniten Tablets, Minoxidil Tablets, Rogaine Topical Solution
spironolactone: Spironolactone tablets
tretinoin: Retin-A (tretinoin)

REFERENCES

1. Hamilton JB. Male hormone is a prerequisite and an incitant in common baldness. Am J Anat 1942; 71: 451–480.
2. Salamon T. Genetic factors in male alopecia. In: Boy A, Morettio G, Frey FR, eds. Baccaredda. Biopathology of pattern alopecia. Basel:Karger:39.
3. Kuster W, Happle R. The inheritance of common baldness: two B or not two B? J Am Acad Dermatol 1984; 11:921–926.
4. Papa CM, Kligman AM. Stimulation of hair growth by topical application of androgens. JAMA 1965; 191: 521–525.
5. Savin RC. The ineffectiveness of testosterone in male pattern baldness. Arch Dermatol 1968; 98:512–514.
6. Chidsey CA, Gottlieb TB. The pharmacologic basis of antihypertensive therapy: the role of vasodilator drugs. Prog Cardiovasc Dis 1974; 27:99–113.
7. Dargie HJ, Dollery CT, Daniel JP. Minoxidil in resistant hypertension. Lancet 1977; 2:515–518.
8. Devine BL, Fife R, Trust Pm. Minoxidil for severe hypertension after failure of other hypotensive drugs. Br Med J 1977; 2:667–669.
9. Burton JL, Marshall A. Hypertrichosis due to minoxidil. Br J Dermatol 1979; 101:593–595.
10. Zappacosta AR. Reversal of baldness in a patient receiving minoxidil for hypertension. N Engl J Med 1980; 303:1480–1481.
11. Seidman M, Westfried M, Maxey R, et al. Reversal of male pattern baldness by minoxidil: a case report. Cutis 1981; 28:551–553.
12. Weiss VC, West DP, Mueller CE. Topical minoxidil in alopecia areata. J Am Acad Dermatol 1981; 5:224–226.
13. Klemp P, Peters K, Hansted B. Subcutaneous blood flow in early male pattern baldness. J Invest Dermatol 1989; 92:725–726.
14. Wester RC, Maibach HI, Guy RH, Novak E. Minoxidil stimulates cutaneous blood flow in human balding scalps: pharmacodynamics measured by laser Doppler velocimetry and photopulse plethysmography. J Invest Dermatol 1984; 82:515–517.
15. Headington TJ. Hair follicle biology and topical minoxidil: possible mechanism of action. Dermatologica 1987; 175(Suppl 2):19–22.
16. Buhl AE, Waldon DJ, Kawabee TT, Holland JM. Minoxidil stimulates mouse vibrissae follicles in organ culture. J Invest Dermatol 1989; 92:315–320.
17. Cohen RL, Alves MEAF, Weiss VC, et al. Direct effects of minoxidil on epidermal cells in culture. J Invest Dermatol 1984; 82:90–93.
18. Uno H. Stumptailed macaques as a model of male-pattern baldness. In: Maibach HI, Lowe NJ, eds. Models in dermatology. Vol 3. Basel: Karger, 1987:159.
19. Uno H, Cappas A, Schlagel C. Cycle dynamics of hair follicles and the effects of minoxidil on the bald scalps of stumptailed macaques. Am J Dermatopathol 1985; 7:283–297.
20. Uno H, Cappas A, Brigham P. Action of topical minoxidil in the bald stumptailed macaque. J Am Acad Dermatol 1987; 16:657–668.
21. Uno H, Cappas A, Brigham PA. Transformation of hair follicles and the therapeutic effect of minoxidil on the bald scalp of stumptailed macaques (Macaca Arctoides). Chronica Dermatologica 1985; 16:565–583.
22. Stern RS. Topical minoxidil—a survey of use and complications. Arch Dermatol 1987; 123:62–65.
23. Tosti A. Topical minoxidil useful in 18% of patients with androgenetic alopecia: a study of 430 cases. Dermatologica 1986; 173:136–138.
24. Headington JT, Novak E. Histological findings in androgenetic alopecia treated with topical minoxidil. Br J Dermatol 1982; 107(Suppl 22):20–21.
25. Vanderveen EE, Ellis CN, Kang S, et al. Topical minoxidil for hair regrowth. J Am Acad Dermatol 1984; 11: 416–421.
26. Novack E, Franz TJ, Headington JT, Wester RC. Topically applied minoxidil in baldness. Int J Dermatol 1985; 24:82–87.
27. De Villez RL. Androgenetic alopecia treated with topical minoxidil. J Am Acad Dermatol 1987; 16:669–672.
28. Shupack JL, Kassimir JJ, Thirumoorthy T, et al. Dose-response study of topical minoxidil in male pattern alopecia. J Am Acad Dermatol 1987; 16:673–676.

29. Rietschell RL, Duncan SH. Safety and efficacy of topical minoxidil in the management of angrogenetic alopecia. J Am Acad Dermatol 1987; 16:667–684.
30. Olsen EA, DeLong ER, Weiner MS. Long-term follow-up of men with male pattern baldness treated with topical minoxidil. J Am Acad Dermatol 1987; 16:688–695.
31. Savin RC. Use of topical minoxidil in the treatment of male pattern baldness. J Am Acad Dermatol 1987; 16: 696–704.
32. Roberts JL. Androgenetic alopecia: treatment results with topical minoxidil. J Am Acad Dermatol 1987; 16: 705–710.
33. Katz HI, Hien NT, Prawer SE, Goldman SJ. Long-term efficacy of topical minoxidil in male pattern baldness. J Am Acad Dermatol 1987; 16:711–717.
34. Kreindler TG. Topical minoxidil in early androgenetic alopecia. J Am Acad Dermatol 1987; 16:718–724.
35. Price VH. Summary. J Am Acad Dermatol 1987; 16: 749–750.
36. Olsen EA, Weiner MS, Amara IA, DeLong ER. Five-year follow-up of men with androgenetic alopecia treated with topical minoxidil. J Am Acad Dermatol 1990; 22:643–646.
37. Spindler JR. The safety of topical minoxidil solution in the treatment of pattern baldness: the results of a 27-center trial. Clin Dermatol 1988; 6:200–212.
38. Spindler JR. Deaths occuring during clinical studies of topical minoxidil. J Am Acad Dermatol 1985; 12: 586–587.
39. Bazzano GS, Terezakis N, Wesley G. Topical tretinoin for hair promotion. J Am Acad Dermatol 1986; 15: 880–883.
40. Ferry JJ, Forbes KK, Vanderlugt JT, Szpujnar GJ. Influence of tretinoin on the percutaneous absorption of minoxidil from an aqueous topical solution. Clin Pharmacol Ther 1990; 47:439–446.
41. Nilsson GE. Measurement of water exchange through skin. Med Biol 1977; 15:209–218.
42. Tagami H, Yoshikuni K. Interrelationship between water-barrier and reservoir functions of pathologic stratum corneum. Arch Dermatol 1985; 121:642–645.
43. Leveque JL, Garson JC, De Rigal J. Transepidermal water loss from dry and normal skin. J Soc Cosmet Chem 1979; 30:333–343.
44. Roenigk HH Jr. New topical agents for hair growth. Clin Dermatol 1988; 6:119–121.
45. Olsen EA, DeLong E. Transdermal viprostol in the treatment of male pattern baldness. J Am Acad Dermatol 1990; 23:470–472.
46. Bertolino AP. Unpublished communication.
47. Bencini PL, Montagnino G, Sala F, et al. Cutaneous lesions in 67 cyclosporin-treated renal transplant recipients. Dermatologica 1986; 172:24–30.
48. Wysocki GP, Daley TD. Hypertrichosis in patients receiving cyclosporine therapy. Clin Exp Dermatol 1987; 12:191–196.
49. Picascia DD, Roenigk HH Jr. Effects of oral and topical cyclosporine in male pattern alopecia. Transplant Proc 1988; 20(Suppl 4):109–111.
50. Gilhar A, Pillar T, Etzioni A. Topical cyclosporine in male pattern alopecia. J Am Acad Dermatol 1990; 22: 251–253.
51. Brest AN. Spironolactone in the treatment of hypertension: a review. Clin Ther 1986; 8:568–585.
52. Stripp B, Taylor AA, Bartter JR, et al. Effects of spironolactone on sex hormones in man. J Clin Endocrinol Metab 1975; 41:777–781.
53. Corvol P, Michaud A, Menard J, et al. Antiandrogenic effect of spironolactones: mechanism of action. Endocrinology 1975; 97:52–58.
54. Pita JC, Lippman ME, Thompson EB, Loriaux DL. Interaction of spironolactone and digitalis with the 5-alpha-dihydrotestosterone (DHT) receptor of rat ventral prostate. Endocrinology 1975; 97:1521–1527.
55. Goodfellow A, Alaghband-Zadeh J, Carter G, et al. Oral spironolactone improves acne vulgaris and reduces sebum excretion. Br J Dermatol 1984; 111: 209–214.
56. Barth JH, Cherry CA, Wojnarowska F, et al. Spironolactone is an effective and well tolerated systemic antiandrogen therapy for hirsute women. J Clin Endocrinol Metab 1989; 68:966–970.
57. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. Br J Dermatol 1985; 112:124–125.
58. Aram H. Treatment of female androgenetic alopecia with cimetidine. Int J Dermatol 1987; 26:128–130.
59. Morales-Alanis H, Brienne MJ, Jacques J, et al. Antiandrogenic activity of a series of des-a-steroid derivatives. J Med Chem 1985; 28:1796–1803.
60. Lookingbill DP, Abrams BB, Ellis CN, et al. The effect of a topical antiandrogen inocoterone acetate (RU882) on acne: results of a multicenter clinical trial. Archives Dermatol 1992; 128:1197–1200.
61. Imperato-McGinley T, Guerrero L, Gautier T, Peterson RE. Steroid 5-α-reductase deficiency in man: an inherited form of male pseudohermaphrodism. Science 1974; 186:1213–1215.
62. Bingham KD, Shaw DA. The metabolism of testosterone by human male scalp skin. J Endocrinol 1973; 87:111–121.
63. Schweikert HU, Wilson JD. Regulation of human hair growth by steroid hormones. I. Testosterone metabolism in isolated hairs. J Clin Endocrinol Metab 1987; 65:188–193.
64. Rittmaster R, Uno H, Povar ML, et al. The effects of N,N-diethyl-4-methyl-3-oxo-4-aza-5 α-androstane-17 β-carboxamide, a 5 α-reductase inhibitor and antiandrogen, on the development of baldness in the stumptailed macaque. J Clin Endocrinol Metab 1987; 65:188–193.
65. Liang T, Heiss CE, Cheung AH, et al. 4-aza steroidal 5 α-reductase inhibitory with out affinity for the androgen receptor. J Biol Chem 1984; 259:734–739.
66. Rasmusson GH, Liang T, Brooks JR. A new class of 5 α-reductase inhibitors. In: Roy AK, Clark JH, eds. Gene regulation by steroid hormones II. Springer Verlag, 1983.
67. Diani AR, Mulholland MJ, Shull KL, et al. Hair growth effects of oral administration of finasteride, a steroid 5 α-reductase inhibitor, alone and in combination with topical minoxidil in the balding stumptailed macaque. J Clin Endocrinol Metab 1992; 74:345–350.
68. Black J. Electrical stimulation of hard and soft tissues in animal models. Clin Plast Surg 1985; 12:243–257.
69. Alvarez OM, Mertz PM, Smerveck RV, et al. The healing of superficial skin wounds is stimulated by external electrical current. J Invest Dermatol 1983; 81:144–148.
70. Bell PW. Prospectus technical report appendix. Vancouver: Current Technology Corporation; 1988; 1.
71. Maddin WS, Bell PW, James JHM. The biological effects of a pulsed electrostatic field with specific reference to hair. Int J Dermatol 1990; 29:446–450.
72. Schwan HP. Hazards from exposure to electrical fields and potentials. IEEE Trans Biomed Eng 1974; 21: 178–191.
73. Gropper CW. Unpublished communication.
74. Toshitani S, Nakayama J, Yahata T, et al. J Dermatol 1990; 17:240–246.

RELATED PROCEEDINGS

1. Board of Patent Appeals and Interferences Decision on Appeal No. 2004-0543, Application No. 10/010,678 (copy previously provided)

2. Merck & Co., Inc. v. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc., No. 04-1313 (D.Del. May 18, 2006) (stipulation of dismissal)

RELATED PROCEEDINGS

Merck & Co., Inc. v. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.- In the United States District Court for the District of Delaware, C.A. No. 04-1313 (GMS), Stipulation of Dismissal, dated May 18, 2006

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 04-1313 (GMS)
	)	
DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.,	)	
	)	
Defendants.	)	

STIPULATION OF DISMISSAL

IT IS HEREBY stipulated by the parties, pursuant to Fed. R. Civ. P. 41(a)(1)(ii), that this action, including all claims, counterclaims, and defenses, is hereby dismissed without prejudice, with each party to bear its own costs, expenses and attorneys' fees incurred in connection with this action.

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